The clinical assessment and treatment of intensive care unit-acquired weakness

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The clinical assessment and treatment of intensive care unit-acquired weakness

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Author statement

I declare that the work contained within this thesis is my own. I have prepared this thesis under the supervision of Dr Nicholas Hart and Professor John Moxham. Gareth Jones and Alexandra Curtis undertook data acquisition in Chapter Three. Dr. Zudin Puthucheary assisted with ultrasound training at the outset of the studies, and contributed to data acquisition for inter-observer agreement in Chapter Four as the second clinician. Victoria MacBean acted as the second reviewer for the systematic review reported in Chapter Five. April Thompson provided valuable research assistance for the study described within Chapter Six.

Patient enrolment was supported by collaboration with clinical colleagues from the Intensive Care Units of St.Thomas' Hospital and King's College Hospital. Healthy subjects were recruited from hospital and research staff, their relatives, and from a bank of volunteers with a registered interest in research participation at both sites.

For Mum, who always knew this would be possible,

and for Dad,

who looks after her now

This thesis is dedicated

in memory of my beloved parents,

Danny and Sally Connolly

"...It's I'll be here in sunshine or in shadow..."

(*Danny Boy*,
Frederick Weatherly, 1910)

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Abstract

Admission to the intensive care unit with critical illness can result in significant and wide-ranging impairments for survivors, which often persist for many years following resolution of the index illness and are now recognised as 'post intensive care syndrome'. One component of this syndrome, peripheral skeletal muscle wasting and dysfunction that develop during critical illness are described as intensive care unit-acquired weakness (ICU-AW) and account for residual deficits in physical functional ability in post ICU patients. This thesis comprised studies examining the clinical assessment and treatment of patients with ICU-AW investigating the Medical Research Council sum-score (MRC-SS) tool, the most commonly reported technique for diagnosing ICU-AW, use of ultrasound to measure peripheral skeletal muscle architecture during critical illness, and exercise-based rehabilitation for critical illness survivors with ICU-AW.

Moderate levels of inter-observer agreement and limited clinical predictive value using the MRC-SS for ICU-AW diagnosis were demonstrated, highlighting the challenges of the volitional manual muscle testing approach. Investigation of ultrasound to assess peripheral skeletal muscle architecture provided data to support technical application of this tool as a potential surrogate marker for strength in ICU patients where direct measurement may be limited. Post hospital discharge exercise-based rehabilitation for critical illness survivors with ICU-AW was explored in a pilot feasibility randomised controlled trial. Whilst no improvement in outcome was evident, process evaluation revealed methodological factors for further investigation in the design and conduct of a larger-scale trial, including development of an intervention effective beyond the extent of natural recovery observed. Follow-up of patients without ICU-AW highlighted the limitations of adopting the MRC-SS threshold to categorise diagnosis and ongoing rehabilitation requirements. A national UK survey revealed failure to implement published guidance on rehabilitation following critical illness following hospital discharge due to lack of funding, resources and managerial prioritisation, and suggests the need for a robust evidence base to support service delivery to address the currently unmet clinical need in this patient population.

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Abbreviations

ICU	intensive care unit
ICU-AW	intensive care unit-acquired weakness
CIM/P/NM	critical illness myopathy/polyneuropathy/polyneuromyopathy
MMT	manual muscle testing
MRC	Medical Research Council
MRC-SS	Medical Research Council sum-score
HHD	handheld dynamometry
ICC	intraclass correlation coefficient
AP	adductor pollicis
ADMF	ankle dorsiflexor muscle force
TwAP or Q	Adductor pollicis or quadriceps twitch tension
MVC	maximum voluntary contraction
CMAP	compound motor action potential
MRI	magnetic resonance imaging
CT	computed tomography
CSA	cross-sectional area
P/ACSA	physiological/anatomical cross-sectional area
EM	early mobilisation
RCT	randomised controlled trial
6MWT	Six Minute Walk Test
NICE	National Institute for Heath and Care Excellence
ISWT	Incremental Shuttle Walk Test
MBS	Modified Borg Scale
VAS	visual analogue scale
SF-36	Short Form-36 version 2 questionnaire
P/MCS	Physical/Mental Component Score
PF	Physical Function domain
MCID	minimum clinically important difference
HADS	Hospital Anxiety and Depression Scale
QMVC	quadriceps maximum voluntary contraction
EMG	electromyography

Tr	potentiated twitch
RF_{CSA}	rectus femoris cross-sectional area
RF_{PCSA}	rectus femoris physiological cross-sectional area
RF_{PA}	rectus femoris pennation angle
ASIS	anterior superior iliac spine
TUAG	Timed Up And Go
STS-5	Sit-to-Stand 5 times
TP/N	true positive/negative
FP/N	false positive/negative
LOS	length of stay
ROC	receiver operating characteristic
P/NPV	positive/negative predictive value
RASS	Richmond Agitation Sedation Scale
EMS	Elderly Mobility Scale
IQR	interquartile range
ICC	intraclass correlation coefficient
UTP	unable to perform
ATP	able to perform
APACHE	Acute Physiology and Chronic Health Evaluation
AUC	area under curve
BMI	body mass index
FFMI	fat-free mass index
SIGN	Scottish Intercollegiate Guidelines Network
NOS	Newcastle-Ottowa Scale
EBRP	exercise-based rehabilitation programme
PR	pulmonary rehabilitation
RM	repetition maximum
MDT	multidisciplinary team
DG	district general hospital
UT	university teaching hospital

Chapter 1 Introduction

1.1 Introduction

Admission to the intensive care unit (ICU) with critical illness can have profound and long-lasting physical and psychological effects for the patient, their family and their care-givers. Frequently, these impairments persist many years beyond resolution of the index illness. Skeletal muscle wasting and weakness occurring during the period of mechanical ventilation and immobilisation associated with ICU admission are considered significant drivers underlying much of the physical impairment observed in survivors of critical illness. Early identification of those patients at most risk of acquiring such muscle dysfunction, commonly known as intensive care unit-acquired weakness (ICU-AW), is essential for delivering targeted rehabilitation and therapeutic interventions. Volitional measures for assessing muscle force are limited in critically ill patients requiring active engagement, cooperation and cognition for optimum performance. However non-volitional measures can be technically challenging in the ICU environment and require skilled personnel for interpretation. Effort-independent techniques with clinical utility for monitoring the trajectory of muscle loss are most likely to be implemented in a widespread and effective manner. Meanwhile, strategies for ameliorating deconditioning and frailty observed in critical illness patients commence within the ICU once clinical stability is achieved. Whilst novel technologies and adjuncts such as electrical stimulation can be considered, typically physiotherapeutic rehabilitation involves a hierarchical progression of functional manoeuvres such as sitting over the edge of the bed, standing and ultimately walking. This concept of early mobilisation has gained an increasing profile and the continuation of exercise therapy and rehabilitation following transfer to the ward and beyond hospital discharge in a seamless rehabilitation pathway is strongly advocated. However, data to support the latter stages of this continuum are lacking, albeit a more focussed exercise approach appears common. In particular, data from randomised controlled trials are limited. Furthermore, despite publication of national UK guidelines to direct this area of clinical practice, widespread implementation remains limited and reflects an inconsistent approach to the ongoing provision of rehabilitation services for post critical illness patients.

1.2 Historical introduction

Skeletal muscle wasting was first described as a syndrome associated with ill and dying patients by Hippocrates, giving rise to the clinical term cachexia (from the Greek *kakos*, meaning bad, and *hexis*, meaning habit or state of being). In the 19th century, William Osler reported the physical manifestation of prolonged sepsis, observing how "the loss of flesh (becomes) more noticeable and the weakness is pronounced" in these severely ill patients [1].

Decades later, the first references to muscle pathology in critically ill patients of the early modern medical era were appearing in the literature. In 1956 Hunter published a report of "neostigmine-resistant curarization", with reference to a cohort of patients in whom weakness and difficulty in liberation from mechanical ventilation following neuromuscular blockade had been observed [2]. The earliest detailed description of a specific myopathic presentation subsequent to critical illness, and the condition now commonly referred to as *critical illness myopathy* (CIM) [3], came in 1977 when MacFarlane and colleagues described the protracted physical deficits observed post status asthmaticus [4]. Electromyographic impairments were evident during the acute phase of ventilator weaning in the absence of affected nerve conduction velocity and during subsequent analysis at 2months, at which stage distal leg muscle weakness remained present. A wealth of research since this first report has substantiated these findings, and further identified the accompanying myopathic alterations supported by muscle histology samples taken on biopsy [5]. *Critical illness polyneuropathy* (CIP) was first described by Bolton and colleagues throughout the 1980s and early 1990s [6-9], with detailed electrophysiological studies outlining reductions in compound motor and sensory nerve action potentials in patients presenting with flaccid, areflexic limbs and failure to liberate from the ventilator.

The terms *intensive care unit-acquired weakness* (ICU-AW) [10] or *paresis* (ICU-AP) [11] have emerged more recently as terms to reflect the clinical weakness observed in critically ill patients prior to classification as either CIP, CIM or in many cases, a combination involving both syndromes. Furthermore, these broader

terms relate more closely to the spectrum of physical and functional impairments associated with critical illness, not unique to an electrophysiological diagnosis.

The origins of rehabilitation for patients with critical illness, and the detrimental effect of prolonged immobilisation can also be traced in historical medicine. With significant foresight, William Dock in 1944 and Richard Asher in 1947 described the deleterious outcomes affecting all bodily systems in acutely ill patients consigned to bed in suitably alarming entitled commentaries "The Evil Sequelae of Complete Bed Rest" and "The Dangers of Going to Bed", respectively [12, 13]. Asher advocated the role of the healthcare practitioner in facilitating early mobilisation and reported perhaps the first evidence of the effect of this practice – namely, fewer post-operative complications and a quicker return to work. The potential advantages of this practice in postoperative patients were later echoed in an editorial published in the *British Medical Journal* in 1948 [14]. Petty [15], an intensivist, later described ICUs of the 1960s where patients requiring mechanical ventilation were awake, alert and sitting out in chairs, engaging with people around them and their environment. In the 1970s, early reports were published on the implementation of portable devices for supporting ambulation in ventilated patients, and the significant clinical benefits achieved including improved weaning [16, 17].

Significantly Asher [12], reflecting on both the physical *and* mental impairments experienced by ill patients almost seventy years ago, described a rehabilitation approach incorporating respiratory weaning, physical exercise and occupational therapy, unaware that this would become the cornerstone of extensive international multidisciplinary research into the management of recovery in critically ill patients over the last decade.

1.3 Acquired critical illness neuromuscular disorders

Neuromuscular dysfunction occurs early during critical illness and gives rise to a number of complications for survivors during the ICU admission and following discharge, including protracted requirements for mechanical ventilation and delayed weaning, increased ICU and hospital lengths of stay and mortality, and

ongoing physical and psychological impairment requiring intensive rehabilitation intervention.

1.3.1 Definitions and classification

Multiple synonymous terminology is used in the literature to describe syndromes of the peripheral nerve and muscle evident in critically ill patients including pathology-specific critical illness myopathy (CIM) [3] and polyneuropathy (CIP) [9], and references for mixed presentations such as critical illness polyneuromyopathy (CINM) [18], and the more global description of intensive care unit-acquired weakness (ICU-AW) [10] (Table 1-1). A more detailed description of the variable taxonomy of critical illness neuromuscular disorders is provided by Stevens *et al* [5], as part of a roundtable meeting of experts in 2009.

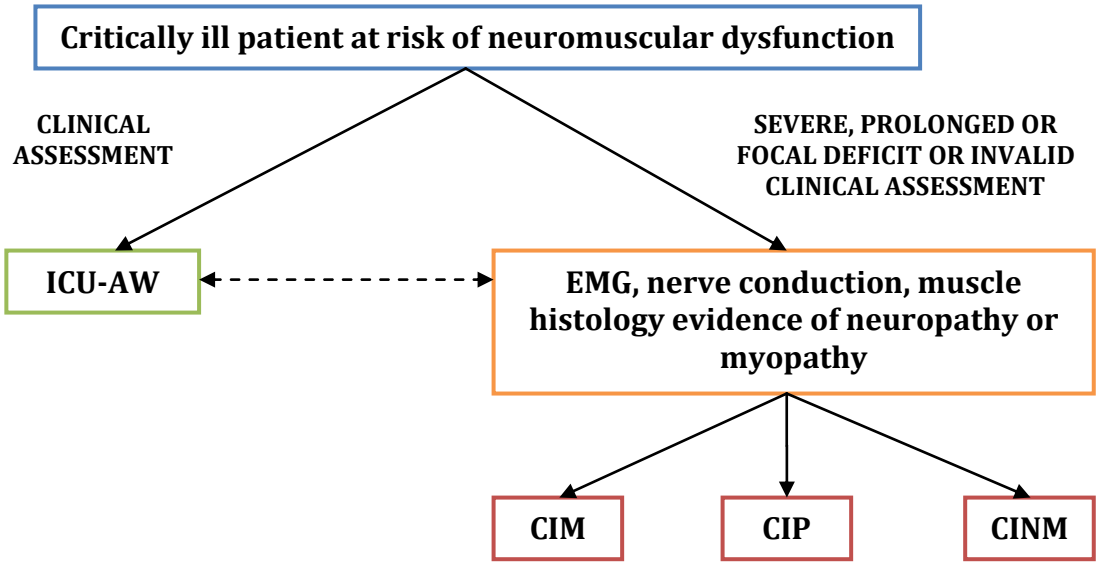
Table 1-1 Terminology describing neuromuscular deficit in critical illness

Term	Definition
Intensive care unit-acquired weakness (ICU-AW)	Clinical weakness attributable to the systemic inflammatory response from index critical illness; no neurologic or metabolic aetiology
Critical illness myopathy (CIM)	Acute primary myopathy with reduced amplitude of sensory nerve action potentials, low-amplitude motor unit potentials +/- fibrillation and reduced excitability on direct muscle stimulation
Critical illness polyneuropathy (CIP)	Sensorimotor axonal polyneuropathy with reduced compound muscle and sensory nerve action potential amplitudes but normal nerve conduction velocity
Critical illness polyneuromyopathy (CINM)	Syndrome involving overlap between both CIP and CIM

[3, 5, 19]

ICU-AW has been suggested as an overarching term to describe critical illness neuromuscular disease with further sub-classifications possible depending on available diagnostic information [5, 19] (Figure 1-1). Use of this term, to simplify a complex clinical condition, has been supported by many to encourage greater identification and reporting of patients presenting with critical illness-related peripheral muscle weakness [19]. If ICU-AW is present, electrophysiological investigations such as electromyography, nerve conduction studies and muscle histology offer data to accurately diagnose CIM, CIP or CINM, albeit the clinical

application of these tests is variable. Indeed, such testing may not be feasible or readily available in all ICUs. More importantly, electrophysiological abnormalities are evident in the majority of patients early on critical illness and thus these diagnoses have limited clinical utility in relation to long-term outcome [5, 20].



Adapted from [5, 19]

Abbreviations: ICU-AW = intensive care unit-acquired weakness. EMG = electromyography. CIM = critical illness myopathy. CIP = critical illness polyneuropathy. CINM = critical illness polyneuromyopathy.

Figure 1-1 Schematic classification neuromuscular disease in critical illness

1.3.2 Diagnostic criteria

ICU-AW is a clinical diagnosis of global peripheral skeletal muscle weakness. Diagnostic criteria for this presentation are embedded in a thorough and detailed clinical assessment undertaken at the bedside, and a process of exclusion of differential diagnoses [5]. Typically patients present with difficulty in weaning from mechanical ventilation and/or profound generalised weakness and impaired mobilisation [19, 21]. Conversely diagnostic criteria for CIM, CIP, CINM relate closely to findings established from electrophysiologic investigations. Table 1-2 summarises diagnostic criteria for these presentations.

Table 1-2 Diagnostic criteria for critical illness-related neuromuscular presentations

ICU-AW	CIM	CIP	CINM
Generalised weakness post critical illness	Criteria for ICU-AW met	Criteria for ICU-AW met	Criteria for ICU-AW, CIP and CIM met
Diffuse, symmetric in nature, of proximal and distal peripheral skeletal muscles with sparing of cranial nerves	SNAP amplitudes >80% of lower normal limit in ≥2 nerves	CMAP amplitudes decreased to <80% of lower normal limit in ≥2 nerves	
MRC sum-score <48/60	Needle EMG in ≥2 muscle groups shows short-duration, low-amplitude motor unit potentials with early/normal full recruitment	SNAP amplitudes decreased to <80% of lower normal limit in ≥2 nerves	
Protracted weaning from mechanical ventilation	Direct muscle stimulation demonstrates reduced excitability in ≥2 muscle groups	Normal nerve conduction velocities without conduction block	
All other causes of weakness excluded	Muscle histology consistent with myopathy (fibre atrophy, necrosis)	Absence of a decremental response on repetitive nerve stimulation	

[3, 5, 19]

Abbreviations: ICU-AW = intensive care unit-acquired weakness. CIP = critical illness polyneuropathy. CIM = critical illness myopathy. CINM = critical illness polyneuromyopathy. MRC = Medical Research Council. CMAP = compound motor action potential. SNAP = sensory nerve action potential. EMG = electromyogram.

1.3.2.1 Limitations of a diagnosis of CIM, CIP or CINM in critically ill patients

Whilst beneficial for providing detailed data to characterise nerve and muscle pathology in critically ill patients, electrophysiological investigation (electromyography, nerve conduction study, muscle biopsy) has a number of clinical and pragmatic caveats. Such invasive testing is costly, has associated clinical risk such as bleeding and infection, and requires high levels of operator skill for implementation as well as clinician expertise for interpretation, therefore rendering general availability of these tests limited. Furthermore, technical difficulties arise associated with the ICU environment including peripheral oedema, signal artefact from other electrical devices, and presence of pressure monitoring lines and devices [5, 22].

Confirming CIM, CIP or CINM has value in diagnostic utility. However, these neuromyopathic conditions often show limited relation to the severity and distribution of ICU-AW. Furthermore, presence of electrophysiologic and histologic abnormalities in critically ill muscle may not clearly translate to other clinically relevant outcomes [11, 20, 23]. Clinical assessment is sufficiently reliable for diagnosing weakness in a critically ill patient; that peripheral muscle and diaphragm electromyography has been shown to not be associated with ICU length of stay or duration of mechanical ventilation, failing to either alter diagnosis or predict outcome, suggests that electromyography may add limited clinically useful information [24, 25].

Of therapeutic importance for the clinician, there is currently no specific treatment for CINM and little known about its long-term outcome and rehabilitative requirements [26]. Hence there is justification for focussing on optimising those aspects of intensive care management that may modify the severity of ICU-AW, such as pharmacotherapy, that directly and indirectly adversely impact on skeletal muscle and early mobilisation, which can be applied to 'high risk' critically ill patients, rather than placing emphasis on an electrophysiological sub-diagnosis [19]. In addition clinical recovery precedes recovery of electrophysiological abnormalities, and changes in peripheral muscle strength are often inconsistent with underlying electrophysiological changes [24, 27]. In essence, even if electrophysiological testing is employed for detailed diagnosis, the value of the test result and repeat measures has limited clinical value.

1.3.3 Risk factors for development of ICU-AW

Lack of experimental models to investigate ICU-AW in isolation has resulted in prospective observational cohort studies and clinical trials providing much of the existing data detailing known risk factors for its development [19]. Illness severity at ICU admission, female gender, systemic inflammation, hyperglycaemia and duration of ICU stay have all been reported as independent risk factors for the development of neuromuscular weakness in critically ill patients [8, 19, 28-32]. Multi-organ failure and prolonged immobilisation have also been widely reported as associated with its onset. Whilst administration of aminoglycoside antibiotic

[30] and corticosteroid [28] medication have previously been suggested as potentially harmful, more recently these have not been proven as independent risk factors [32]. Furthermore, a recent integrative review of the evidence related to use of neuromuscular blocking agents in modern critical care practice concluded that use of these drugs, in general, was less of a risk factor for the development of ICU-AW [33].

1.4 Measurement of peripheral skeletal muscle strength in critically ill patients

Quantitative assessment of peripheral skeletal muscle strength is necessary for establishing ICU-AW and can assist in monitoring progression and predicting outcome in critically ill patients, in particular regarding physical functional performance and ongoing rehabilitation requirements. A number of available measurement techniques have been reported including both volitional and non-volitional methods.

1.4.1 Volitional assessment of peripheral skeletal muscle strength

Routine measurement typically involves a process of manual muscle testing (MMT), evaluating the magnitude of force generated during a maximum voluntary contraction. Specific cut-off values have been identified for ICU-AW diagnosis. Sequential scores may be used to longitudinally chart muscle strength in critically ill patients throughout their admission, and following ICU discharge.

1.4.1.1 Medical Research Council Sum-score

One of the most commonly reported MMT techniques in the literature for determining ICU-AW is the Medical Research Council sum-score (MRC-SS). Based on the MRC scale for assessing muscle strength [34], modification and development in critically ill patients, more specifically those patients with Guillan-Barré syndrome, resulted in refinement to six functional upper and lower limb muscle groups (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, ankle dorsiflexion) [35]. Patients are assessed in either supine or

seated positions, and muscle groups are assessed bilaterally on a scale ranging from 0 (no visible contraction, no strength) to 5 (normal power), producing composite scores ranging from 0 (complete paralysis) to 60 (normal strength). An MRC-SS of less than 48 out of 60 i.e. a score of 4 or less out of 5 in each muscle group assessed, is considered diagnostic of ICU-AW [11, 36, 37], with scores of less than 36 classified as severe weakness [38]. More recently, a collapsed four-point scoring system has been developed (0=paralysis, 1=severe weakness, 2=slight weakness, 3=normal power) to minimise disparity in differentiating between levels in the earlier MRC-grading system, but to date its use has been restricted to neurological conditions with further validation required in the critically ill population before it can be considered in the ICU population [39].

Using the commonly reported MRC-SS cut-off of less than 48 out of 60, a number of prospective studies have reported prevalence of ICU-AW ranging between 24% and 65% [11, 30, 37, 40]. Furthermore, a diagnosis of ICU-AW has been shown to be associated with prolonged weaning, delayed rehabilitation, increased hospital length of stay and mortality in both the ICU and hospital [11, 29, 30, 36, 37, 40-43], albeit one of these studies assessed the severe weakness (<36/60) threshold [43].

1.4.1.2 Dynamometry

Dynamometry is an alternative form of MMT used for measurement of strength in critically ill patients. Adopting standardised procedures for operator implementation, dynamometry is a valid and reproducible technique [44] which can be used during both ICU admission and following discharge [36, 45]. Many devices are lightweight, small and portable increasing their clinical usefulness. A direct relationship has been demonstrated between handheld dynamometry used to measure grip strength, and ICU-AW measured using the MRC-SS; ICU-AW was diagnosed at a cut-off level of 11kg-force for males and 7kg-force for females [36]. Hence, grip strength may offer a quick and simple alternative to comprehensive manual muscle testing with the additional benefit of data detailing the normal range based on gender and age [44, 46, 47].

1.4.1.3 Limitations of volitional peripheral skeletal muscle testing

Whilst appealing for a variety of clinical and pragmatic reasons, the use of MMT to diagnose ICU-AW in critically ill patients has a number of caveats. The volitional nature of testing restricts ability to distinguish true loss of muscle strength from poor motivation and impaired cognition. Whilst positive results confirm intact muscle strength, inability to perform the test or scoring a low value can be influenced by a number of causal factors, including non-muscular related as well as submaximal effort. Extraneous circumstances, such as pain and level of analgesia, level of sedation, arterial monitoring and venous access lines, patient motivation and compliance with assessment influence test outcome, can adversely affect validity and reliability of results. Waak *et al* [48] broadly summarise the muscle strength measurement bias as arising from an interaction between factors relating to subject cooperation, technical considerations, pharmacological paralysis and regional barriers.

Screening for awakeness

When performing MMT patients must be sufficiently awake, alert and cognitively intact to follow the instructions necessary for testing each muscle. Screening tools can facilitate assessment of this such gauging patient response to simple commands such as 'Open your eyes' or 'Nod your head' [11, 36, 37], and ensuring sedation scores are within acceptable and appropriate levels for testing [49]. Clinicians must be confident that patients perform their maximum volitional effort in the correct testing position, albeit this may not be feasible within the ICU environment.

Sensitivity of the MRC grading scale

Ordinal and nonlinear in nature, the MRC scale for grading muscle strength is flawed in construct with differential sensitivity evident across the range of scores which may result in a ceiling effect [38, 50]. For example, scores at level 3 or below incorporate gravity as an objective reference quantity, whereas for levels 4 and 5, quantity of additional resistance is not specified nor is it measured during

testing. Grade 4 strength may encompass a wide range of muscle strength, and establishing a true 'normal' (level 5) for a critically ill patient is challenging. In essence, discriminant ability of the scale above level 3 is poor [51], and validity and reliability depend upon the context of the interaction between clinician and patient, and the experience and individual judgement of the clinician in delivering and interpreting the assessment [52]. Subtle changes in muscle strength may remain undetected by manual muscle testing despite significant electrophysiological changes [27], nor does the MRC-SS include distal muscle groups such as those in the hand and fingers that may show early signs of weakness [5].

Protocol for muscle group assessment

When conducting MRC-SS assessments muscle groups can be assessed either isometrically, at one point in range, or through range of movement [53], but this is not clarified in the original instructions [35] nor consistently documented as part of the testing procedure. Not only could this potentially lead to discrepancies in isolated measurements, but limitations in comparison of values scored longitudinally and involving more than one clinician. Furthermore these two techniques are not comparable and cannot be used interchangeably. Reliability and agreement for the diagnosis of ICU-AW have been reported as higher for the isometric technique [54], however, it is vital that clinicians adopt a standardised testing protocol for all aspects of testing including patient and examiner position, contraction time, instruction and encouragement given, number of repetitions and duration of rest periods, in addition to method of strength assessment [55]. Written as well as visual descriptions of the performing the isometric testing process have been reported [38, 56, 57].

In patients able to achieve anti-gravity strength, dynamometry has been suggested as a more sensitive tool for assessment of muscle strength [55]. However, there are variations in the testing process for various muscle groups which are important to consider, and again standardisation of protocol is important. Handheld dynamometry for grip strength involves the 'make test' where the examiner holds the device steady to match patient exertion (or the patient holds

the device themselves depending on the model used), as opposed to the 'break test' used for other peripheral skeletal muscle groups, where the examiner exerts force sufficient to overcome the patient's effort and they are no longer able to maintain the testing position [58]. One limitation of this technique is reliance on the ability of the tester to demonstrate this level of resistance at the upper ranges of patient ability. Recent data suggest dynamometry may be most reliable at mild to moderate strength levels, similar to that observed at MRC levels 3-4 [50].

Clinician agreement

Contrasting results for inter-observer agreement of MMT have been reported. In stable outpatients recovering from critical illness high levels of inter-rater reliability between clinicians for MRC-SS testing have been demonstrated (intraclass correlation coefficient (ICC) 0.99) [59]. Overall Kappa scores for agreement of the binary outcome of ICU-AW diagnosis also indicated very good agreement albeit confidence intervals were wide (Kappa (95%CI) 0.88 (0.44-1.0)) [59]. Weaker levels of agreement for ICU-AW diagnosis were evident when testing was applied to a mixed cohort of more acute patients within the ICU and following discharge to the ward, although wide variability in scores was again evident (Kappa (95%CI) 0.76 (0.44-1.0)) [60]. Furthermore, only a third of patients in whom testing was attempted whilst in the ICU were able to complete the measure, with only fair agreement for ICU-AW diagnosis reported (Kappa 0.38). Higher levels of agreement were seen in a larger cohort of patients tested whilst still in the ICU (Kappa 0.68±0.09), albeit these were chronically critical ill patients with ICU length of stay of approximately three weeks, and less than one third remaining mechanically ventilated at the time of testing [38]. In this study, inter-observer agreement for hand-held dynamometry (HHD) was greater than for MRC-SS, although cut-offs for diagnosis of ICU-AW using HHD [36], were not examined. Finally Baldwin *et al* [50] demonstrated ranges of inter-rater consistency (ICC (95%CI) 0.78 (0.32-0.93) to 0.95 (0.84-9.98)) and test-retest agreement (0.82 (0.39-0.94) to 0.92 (0.78-0.97)) of HHD for three major muscle groups (handgrip, elbow flexion and knee extension) [50]. Whilst beneficial for validation of the dynamometry technique, only handgrip thresholds for diagnosing ICU-AW have

been established, and these were, as previously, disappointingly not analysed in this dataset.

Relationship with physical function and clinical outcome

There are currently no data to confirm a relationship between ICU-AW and physical functional ability. Whilst the threshold for MRC-SS of less than 48 out of 60 provides a potentially logical representation of 'functional' muscle weakness i.e. to meet this score muscle groups fail to demonstrate movement against resistance, clinically important levels of ICU-AW have yet to be determined and subclinical levels currently may be missed [21]. Further studies in this area will define clinically significant weakness, as deficits in physical functional performance may be present in patients scoring greater than 48 out of 60. This has the potential to significantly inform provision of rehabilitation intervention to those with demonstrable impairment regardless of ICU-AW diagnosis based on MRC-SS assessment. Performance of a physical functional task is the coherent combination of complex motor tasks, whereas MMT assesses individual isolated muscle actions and therefore a linear relationship between these two variables is unlikely. In a cohort of surgical ICU patients, for every one unit increase in strength, a 5% relative decrease in the odds of mortality has been shown [61] although this did not examine the clinical outcome in terms of the ICU-AW threshold value. Importantly, the clinical utility and predictive value of manual muscle testing, in particular the MRC-SS, for diagnosis of ICU-AW requires further investigation.

1.4.2 Non-volitional assessment of peripheral skeletal muscle strength

Non-volitional techniques to assess peripheral skeletal muscle strength depend on supra-maximal external stimulation, via electrical or magnetic means, of the motor nerve supply to the muscle. In this way, the muscle force generated is not dependent on volitional patient effort, the influences of cooperation, motivation and external environmental factors are removed. Reliable and objective values can therefore be obtained in patients who may be sedated and mechanically ventilated. Available techniques include measurement of adductor pollicis (AP) force using ulnar nerve stimulation [23, 62, 63], quadriceps force elicited by femoral nerve

stimulation [64, 65] and ankle dorsiflexor muscle force (ADMF) evoked by peroneal nerve stimulation [65-67].

1.4.2.1 Adductor pollicis muscle strength and ulnar nerve stimulation

The technique of measuring AP force involves the use of a hand board to immobilise during stimulation the hand and forearm in supination [62, 63, 68]. A strain gauge, mounted on the board and connected to a metal loop positioned around the proximal phalanx of the thumb (in abduction) by an inextensible metal chain, transmits force generated. To minimise rotation of the wrist the hand and forearm are encased in a rigid plastic splint with access to the ulnar nerve for stimulation.

In a study comparing a cohort of patients with sepsis and multiorgan failure to healthy subjects after limb immobilisation, Eikermann *et al* [23] demonstrated significant reductions in AP force in the critically ill cohort (20±16 vs. 65±19N; $p<0.01$). The characteristics of muscle function assessed included the force generation at variable stimulus frequencies ranging from 10-80Hz (force-frequency relationship), single twitch muscle contraction and half relaxation times (time elapsed for 50% decrease in force from peak following final stimulus pulse at 10Hz) as well as fatigue at low frequency stimulation (20min of intermittent titanic stimulation achieving 50% maximum AP force).

Whilst offering one method for non-volitional assessment of muscle force production, tetanic motor nerve stimulation at high frequencies can be painful, resulting in limited patient tolerability [62]. An alternative is assessment of muscle contractility involving measurement of the force response to supramaximal stimulation i.e. where further increases in stimulation intensity do not elicit production of larger forces. Adductor pollicis twitch tension (TwAP), measured using both electrical and magnetic stimulation, was found to be significantly reduced in critically ill patients compared to age-matched healthy controls (n=20 in each arm, 4.2 (2.2-6.7)N vs. 7.1 (4.4-9.8)N; $p<0.01$) [63]. Similar significant differences between ICU patients and healthy controls for TwAP were also reported by Pickles *et al* from a larger cohort [69] (3.6±1.2N vs. 7.3±2.4N;

p<0.001). Weakness assessed by TwAP developed within the first week of ICU admission and this remained low throughout the three-week ICU admission period of measurement.

TwAP has a number of advantages as a measure of muscle strength. Isometric twitch tension such TwAP assumes the relationship between force produced by the single twitch and the force produced by high frequency stimulation and the resultant tetanic contraction (or truly maximal MVC) is constant. For adductor pollicis, the range of TwAP/MVC ratios is narrow, confirming this relationship [63]. In addition, magnetic stimulation is preferable as the stimulating coil requires less accuracy for placement and less surface pressure. Magnetic stimulation is virtually painless as the firing threshold for motor fibres is much less than for sensory fibres [70]. Furthermore, stimulating currents are produced *in situ* such that their intensities can be very low, as opposed to electrical stimulation techniques that require relatively high stimulating currents to overcome skin resistance [71]. Finally, the TwAP technique is well tolerated, even in critically ill patients, and has clinical utility causing minimal disruption to patient position or interacting with treatments.

1.4.2.2 Quadriceps muscle strength and femoral nerve stimulation

The quadriceps is an important muscle for locomotion and other functional activities. Polkey *et al* [64] described a technique of supramaximal magnetic stimulation of the femoral nerve using a 70mm figure-of-eight coil placed high in the femoral triangle, lateral to the femoral artery and over the femoral nerve, which was found be simple to perform, painless and reproducible. Quadriceps twitch tension (TwQ) is determined following supramaximal stimulation, and the mean TwQ/MVC ratio has been reported as 0.15 for both men and women [72] This technique has been used to demonstrate quadriceps muscle contractility in healthy subjects and patients with chronic respiratory disease [64, 65, 73]. However, the measurement process involves subject positioning in supine on a bespoke testing bench with knee flexion at 90^{o}. Quadriceps force is measured by an inextensible strap positioned around the ankle joint and connected to a strain gauge. For these reasons it is rarely feasible to conduct these measurements in

critically ill patients in the ICU environment. Furthermore, supramaximal electrical femoral nerve stimulation is feasible but technically challenging with limited reproducibility, and transcutaneous electrical stimulation activates only a fraction of muscle via peripheral femoral nerve branches and hence is submaximal making this approach less clinically helpful in the ICU [74].

Only one group have recently published data on non-volitional assessment of quadriceps force in critically ill patients in the ICU. Vivodtzev et al [75] and colleagues assessed 13 consecutive sedated and mechanically ventilated patients with organ failure, and then repeated measurements after awakening in nine of the cohort. Mean Twq was 1.8±1.3kg for the whole group of patients. TwQ was double in COPD patients ()compared to ICU patients ($p < 0.001$), and four times higher in healthy subjects ($p < 0.001$). There was no significant difference in TwQ between ICU patients whether sedated or awake.

1.4.2.3 Ankle dorsiflexor muscle strength and peroneal nerve stimulation

Ankle dorsiflexor muscle force (ADMF) can be measured using peroneal nerve stimulation. In critically ill patients mechanically ventilated for seven days, peak torque has been shown to be significantly reduced (median (IQR) 3.3 (2.5)Nm vs. 4.1 (2.0)Nm, $p=0.0003$ for single pulse stimulation; similarly significant results for double, triple and quadruple pulse stimulation), contraction time significantly reduced (104 (37)ms vs. 116 (53)ms, $p=0.0001$), and half-relaxation time significantly increased (115 (45)ms vs. 110 (31)ms, $p=0.01$) compared to healthy controls [66]. In addition, Seymour *et al* [65] reported tetanic contraction force at 100Hz electrical stimulation equal to that obtained during MVC manoeuvres, and tolerability of the technique in healthy subjects and patients with chronic respiratory disease. Access to the site of assessment, the distal lower limb, is often unrestricted in critically ill patients and measurement requires no alteration in patient position, clinical advantages to ADMF measurement.

1.4.2.4 Technical considerations

Standardisation of non-volitional techniques for measuring muscle strength in critically ill patients is vital for optimising reliability and validity of data acquisition, given its relative advantages over volitional methods. Stimulation intensity must be supramaximal to result in contraction of the entire muscle. For electrical stimulation this is typically 5-20% above that required for maximal response [20] indicated by a plateau in CMAP amplitude or force response. Stimulation intensity depends on both the current applied and the pulse duration. Adequate skin preparation is a further prerequisite of nerve stimulation, involving abrasion and cleansing to ensure acceptable electrical contact. Correct placement of electrodes ensures stimulation of the desired nerve only, and selection of appropriately sized electrodes ensures optimal current density. Muscle preload directly affects force production and should be standardised throughout the protocol either through setting a specified preload via the force transducer, or defining joint position during measurement [20].

Muscle temperature significantly influences skeletal muscle function [76]. Low skin and muscle temperature can be common in septic critically ill patients with impaired peripheral circulation, which can be further exacerbated by vasoconstrictive medications. Strategies to maintain a constant muscle temperature during testing are necessary to minimise variation in mechanical muscle properties influencing results [77].

Potentiation is the phenomenon by which preceding muscle contraction (either volitional or non-volitional in origin) enhances or reinforces the response to stimulation, resulting in greater force production [78, 79]. Potentiation is often most evident at low stimulation frequencies, such as the single twitch response. In these circumstances, resting the muscle completely for 20 minutes prior to testing produces stable, unpotentiated twitch responses, whilst a standard protocol involving 30 second intervals between twitches can avoid twitch-on-twitch potentiation [63]. Consideration must be given to avoid trains of stimuli that cause fatigue in themselves.

1.4.2.5 Limitations of non-volitional peripheral skeletal muscle testing

Non-volitional techniques for assessing muscle force remove volitional influences and, if a standardised approach is adopted, can produce robust data. However, expensive specialist equipment is required to perform these measurements with trained personnel required for their implementation and analysis of the results. In addition, there are practical limitations to testing all muscle groups in critically ill patients within the ICU. Few normative data for comparative purposes exist, and it remains uncertain which peripheral skeletal muscle group or single muscle, if any, best reflects global muscle weakness. Indeed, patients with critical illness related skeletal muscle weakness tend to demonstrate proximal to distal weakness, suggesting that this pathological process lacks uniformity across all skeletal muscles

1.4.3 Summary

Both volitional and non-volitional methods for the assessment and measurement of peripheral skeletal muscle strength are available for use with critically ill patients. Each mode of assessment has relative advantages, but neither is without clinical, technical or pragmatic limitations. Simple, clinically pragmatic, but also effort-independent and objective alternatives are required to monitor the trajectory of peripheral skeletal muscle dysfunction during critical illness. More recently, ultrasound of peripheral skeletal muscle architecture e.g. cross-sectional area has emerged as a commonly reported potential technique for this purpose.

1.5 Ultrasound for assessment of peripheral skeletal muscle during critical illness

B-mode ultrasound of peripheral skeletal muscle architecture has increasingly been used as a tool for measuring muscle dysfunction in critically ill patients [80-83]. It has a number of beneficial properties for this purpose, and in addition to the machine being widely accessible with a large proportion of ICUs commonly using ultrasound for venous line and chest drain insertion, it has become an inexpensive, quick, simple and portable technique. Furthermore, it is effort-

independent, free of ionising radiation, can be performed at the bedside, and with training can be implemented by non-specialist clinicians. For these reasons it has the potential for widespread clinical applicability. Significantly ultrasound has been highlighted as a valid and reliable alternative to the 'gold standard' of magnetic resonance imaging (MRI) [84], with recent improvements in ultrasound technology producing muscle images of much greater resolution than typical MRI, therefore making the ultrasound technique a valuable tool for clinical and research purposes [84, 85]. Previous data have shown that ultrasound measurements of quadriceps rectus femoris muscle cross-sectional area in healthy subjects and patients with chronic respiratory disease not only correlate with volitional (quadriceps maximum voluntary contraction, $r=0.80$, $p<0.001$ and $r=0.78$, $p<0.001$ respectively) and non-volitional (quadriceps twitch tension, $r=0.72$, $p<0.001$ and $r=0.69$, $p<0.001$ respectively) measures of quadriceps strength, but also with similar values of cross-sectional area acquired via computed tomography (CT) (intraclass correlation coefficient=0.88), another common scanning process but one which involves radiation exposure [73]. However, similar data are currently lacking in the critical illness population. Nonetheless, ultrasound has been used as a practical alternative to MRI and CT to provide real-time data on a range of peripheral skeletal muscle architecture features including muscle cross-sectional area, muscle layer thickness and echo intensity in critically ill patients [81-83, 85, 86].

1.5.1 Principles of ultrasound

Ultrasound imaging is based on the principles of sound-waves and the echoes produced. A specific ultrasound transducer emits high frequency sound waves; the image created depends upon analysis of the temporal and acoustic properties of the returning echoes [87, 88]. Most biological tissues are comprised mainly of water such that they both reflect and transmit a proportion of the sound waves delivered. When the ultrasound beam encounters tissues with different acoustical properties e.g. muscle, fascia, or bone, the result is a reflection of the sound waves, termed acoustical impedance. Energy reflected from a tissue assists in generating an image of its boundary whereas the transmitted sound penetrates deeper to

facilitate further echo delineation [88]. Hence ultrasound has the potential to map both superficial and deep tissue layers.

The final image produced using ultrasound results from complex computer analysis of the returning echoes [87-89]. Pixel location is determined by the time difference between sending and receiving each relative sound wave, such that those returning earliest are from closer structures, and those returning later, from more distant locations. Echo intensity, the 'grey value' of the image, is determined by the number of returning echoes per square area. Amplitude of sound waves determines image brightness. However, as sound waves lose power with depth of penetration, those travelling from deeper tissues may require further amplification to account for this energy dissipation, known as time-gain compensation. Additional modifications to generate ultrasound images include signal rectification, compression and subtraction akin to the filtering processes involved in electrophysiological signal management. Finally, ultrasound image resolution is directly proportional to sound frequency, whereas depth of penetration is inversely proportional. Hence higher frequency probes can image more superficial structures with greater detail. Both linear and curvilinear probes are available for imaging peripheral skeletal muscle [89].

1.5.1.1 B-mode ultrasound imaging

B-mode ultrasound imaging produces cross-sectional images of tissues and organ borders [90]. In keeping with the main principles of all ultrasound images, it is constructed of the echoes generated by reflection of ultrasound waves from different tissue boundaries. The brightness of the image at each echo point is related to the amplitude of each echo, giving rise to the term B-mode, or 'brightness' mode.

B-mode images closely reflect the anatomical view that might be observed if the body were dissected in that same plane. Abnormal anatomical boundaries indicating pathology can often be identified. B-mode images are often produced by linear transducer arrays i.e. a large number of small transducers arranged in a straight line, that offer a wide, rectangular field of view and are useful for

superficial structures. Curvilinear probes operate in the same manner, albeit the array of transducers along the front face of the probe is arranged in a curve, as opposed to a straight line, and have the additional advantage that the field of view becomes wider with depth.

1.5.2 Assessment of peripheral skeletal muscle architecture using ultrasound

Muscle has fairly distinct sonographic features in comparison with surrounding structures. Normal muscle appears with low echo intensity i.e. relatively black, and divided by sheets of echogenic perimysial connective tissue resulting in a speckled appearance in the transverse plane, whereas in the longitudinal plane, hyperechoic lines are visible forming a pennate structure [87, 91]. The epimysium bordering the muscle is highly echogenic meaning that the outline of a muscle can easily be identified. Bone echo is strong and distinct in healthy subjects, with anechoic bone shadow evident underneath, and this can provide a useful reference structure for identification of certain muscles [88].

A number of characteristics of muscle architecture can be assessed using ultrasound. By marking the inner echogenic muscle border muscle size in the form of both *cross-sectional area* (CSA, also referred to as anatomical cross-sectional area) and *muscle layer thickness* can be measured using either in-built online, or offline software. The same process can be utilised in the evaluation of *muscle echo intensity*, a measure of the grey-scale of the image and which may reflect muscle composition. Echo intensity can also be scored subjectively using a visual grading scale (the Heckmatt score [92]), or simply by describing the distribution of echo intensity within a muscle as either homogenous or inhomogenous. However whilst visual evaluation provide useful information, it is acknowledged that these subjective forms of assessment are less reliable demonstrating weaker inter-observer agreement. Objective scoring, given that it is quick to perform with greater accuracy, should be used where possible. Finally, muscle images obtained longitudinally through the muscle, permit measurement of *pennation angle* (the angle of insertion of muscle fibres into the muscle aponeurosis). Provided

reference markers of known distance are marked on images at the time of acquisition, all these parameters can be measured offline following assessment.

Measurement points for ultrasound of quadriceps muscle architecture include 50% muscle length [93, 94], mid-point between greater trochanter and lateral knee joint line [95, 96], three-fifths distance from anterior superior iliac spine (ASIS) and superior patellar border[73], half femur height [97], two-thirds distance from ASIS and superior patellar border [82, 85], and mid-point between ASIS and superior patellar border [82]. This lack of standardisation of measuring points between studies restricts comparison between results.

1.5.2.1 Physiological cross-sectional area

Physiological cross-sectional area (PCSA) is a measure derived from the anatomical cross-sectional area and pennation angle of a muscle. PCSA was developed to account for the complex geometry of muscle fibre arrangement that results in measurements taken in anatomical planes potentially underestimating the true force-generating capacity of the muscle by not accounting for the cross-sectional area of all individual muscle fibres [98]. PCSA is defined as the total cross-sectional area of all muscle fibres at right angles to their long axes [94, 99, 100].

Muscle fibre arrangement can be inconsistent between muscles of different sizes despite similarities in muscle fibre diameter, hence estimations of force-generating capacity cannot be estimated from muscle fibre diameter alone as fibre arrangement is an important contributing factor [98]. The majority of human skeletal muscles demonstrate a pennate arrangement whereby muscle fibres insert at angles relative to the force-generating axis of the muscle, termed the pennation angle [94, 99, 101]. The quadriceps muscle is an example of such a muscle arrangement. An alternative is a parallel, or longitudinal architecture in which muscle fibres run parallel to the muscle length [98].

The anatomical CSA of a muscle is that cross-sectional area measured at an angle perpendicular to the force-generating axis in the anatomical plane. In a parallel-

fibred muscle this equates to the PCSA, as the anatomical CSA will transect all muscle fibres at right angles [102]. In a pennate muscle, the anatomical CSA will only cross a number of fibres and hence is disproportionate to PCSA [98, 102]. In order to calculate PCSA, the following equation is used

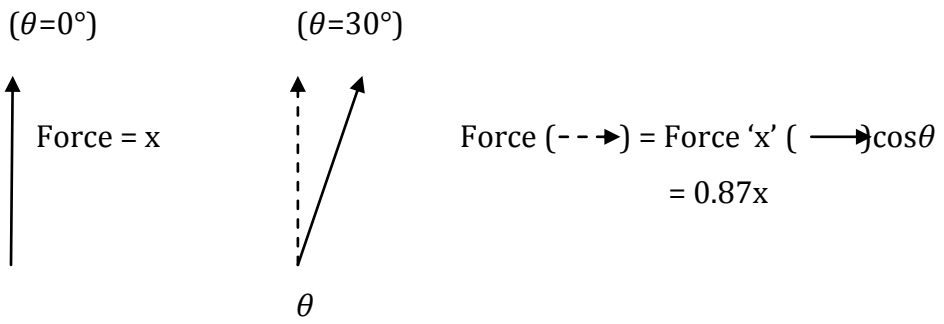
$$PCSA\ (cm^2) = ACSA\ (cm^2)\ cos\theta$$

where θ is pennation angle [94, 98], and cosine of pennation angle normalises fibre angulation to the line of action of the muscle [99].

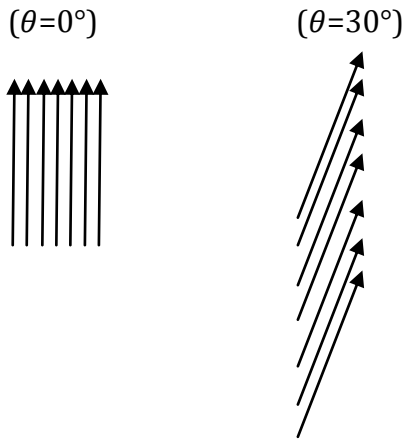
Theoretically, muscle fibres generating force with a pennation angle of 0° i.e. parallel muscles, will transmit all that given force along the muscle axis whereas a pennate arrangement of muscle fibres will result in a loss of force production at the tendon as this force will be proportional to the cosine of the pennation angle [97, 98]. Although muscles appear to have been designed with a biological flaw that results in a loss of usable force-generating capacity, the design represents a 'space-saving strategy' as if all muscles demonstrated parallel fibre arrangement this would preclude their location in a large number of sites throughout the body [98]. Hence, whilst muscle fibres arranged such that there is a pennation angle has an 'energy cost' in terms of force generation, this allows more contractile units to be sited in parallel for a given ACSA [97, 98] (Figure 1-2).

That said, a complex relationship exists between force production at the tendon, the amount of contractile material and angle of pennation [97]. Aagaard *et al* [94] report that pennation angles up to an upper limit of 45° contribute to producing PCSAs that are proportional to the maximum force-generating capacity of a muscle, but despite their suggestion that pennation angle could influence force generation at any given anatomical CSA this association has not been found by other authors [97]. In addition, the relationships described thus far regarding pennation angle and PCSA assume the muscle is in a resting state. Factors such as alteration of pennation angle during contraction and muscle fibre rotation between the aponeurosis and axis of movement may alter values obtained and hence, any relationships between these parameters [98, 99]. Furthermore, no data have reported the potential effect of anthropomorphic factors on pennation angle.

A. Effect of pennation



B. Effect of fibre packing



A. Schematic representation of effect of pennation angle on force production. Fibres oriented parallel to force-generating axis transmit all force in that direction. In this example, a pennation angle of 30° results in fibres transmitting force equal to cosine of the pennation angle i.e. 0.87 or 87%.

B. Pennation can increase the relative amount of force-generating material into a given anatomical cross-sectional area compared to that of a muslce with fibres arranged in parallel.

(adapted from [98])

Figure 1-2 Effect of muscle fibre pennation

1.6 Summary

Ultrasound of peripheral skeletal muscle is an effort-independent technique with the potential for widespread clinical utility for monitoring the trajectory of muscle dysfunction during critical illness, including from the point of ICU admission, with the advantage that a range of characteristics of muscle architecture can be measured. Establishing inter-observer agreement between clinicians for the

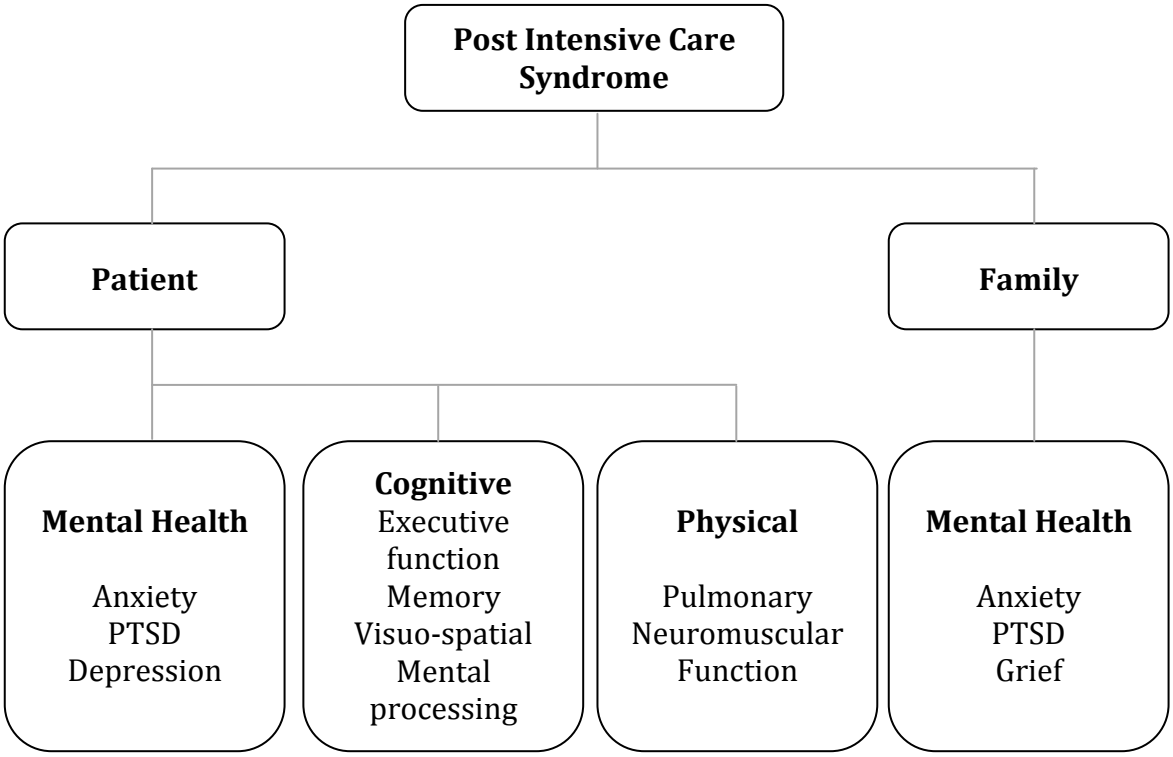
technique will facilitate this process. In addition, previous data reporting a relationship between anatomical cross-sectional area and muscle force suggest the validity of ultrasound measurements as a surrogate where force cannot reliably be measured. The concept of physiological cross-sectional area may provide more clinically useful data, but this requires further investigation. As ultrasound emerges as a popular research technique utilised in observational studies of critically ill patients, a systematic review and evaluation of the available data is important in order to assist in standardising measurement protocols and identifying the characteristics of peripheral skeletal muscle architecture commonly employed to monitor muscle wasting.

1.7 Post intensive care syndrome and rehabilitation for survivors of critical illness

Advances in modern intensive care medicine have resulted in greater survival rates from an admission to the ICU with critical illness, including many patients with complex and chronic co-morbidities. As a consequence, the prevalence of reported impairment in survivors of critical illness has grown significantly. The volume of evidence from observational follow-up studies of post ICU patients is extensive, and characterises the varying and often pronounced morbidity in this population including physical and functional [103-108], cognitive [109-112], psychological [113-115] and health-related quality of life [116-119]. In addition, data have been collected examining the healthcare utilisation and socioeconomic impact of critical illness [103, 120, 121], and to consider the burden experienced by family and care-givers [122-124].

This spectrum of impairment following critical illness has recently been described as 'post intensive care syndrome' [125], a concept designed to encompass the multi-faceted nature of post ICU disability (Figure 1-3). Importantly, follow-up of this population ranges from six months [126-128] to 5 years [105, 116, 129] providing valuable data on the trajectory of recovery for these patients which may assist in the timely delivery of appropriate rehabilitation strategies [130]. Indeed it has been suggested that even longer-term follow-up beyond 5 years may be required to fully appreciate the challenges associated with critical illness

survivorship that may not become apparent during the short to medium-term [131].



(adapted from [125])

Abbreviations: PTSD = post traumatic stress disorder

Figure 1-3 Conceptual diagram outlining post intensive care syndrome

1.7.1 Rehabilitation following critical illness

Rehabilitation is an integral component in the recovery of survivors of critical illness [125, 132-134]. In order to address the complexity and magnitude of symptoms present in patients, a comprehensive multimodal and interdisciplinary rehabilitation package is required [125, 135]. Exercise-based rehabilitation is advocated in the management of ICU-AW and the physical and functional disability arising from muscle wasting and weakness secondary to critical illness. Data have reported the effectiveness of exercise-based interventions delivered at all three stages of the patient pathway; within the ICU, following transfer to the ward and post hospital discharge. In the UK, rehabilitation following critical illness has been profiled by the publication of guidelines in 2009 by the National Institute for Health and Care Excellence (NICE) [136], and the emphasis towards a seamless

transition of care and delivery of rehabilitation for patients across the spectrum of critical illness from ICU admission to recovery in the community.

1.7.1.1 Early mobilisation in the ICU

Early mobilisation (EM) of patients within the ICU has received significant interest in recent years [137-142], with a number of quality improvement projects reported to enhance and develop clinical services [143-147]. Early mobilisation can be defined as "...the intensification and early application of physical therapy administered to critically ill patients" typically commencing within the first forty-eight hours of ICU admission following achievement of clinical stability [148]. The aim is to preserve or restore the integrity of musculoskeletal strength and function, and minimise physical and functional impairment and disability during recovery. Shifts in practice within intensive care medicine, in particular with regard early weaning of patients onto spontaneous modes of ventilation, have facilitated the integration of EM into the management of critically ill patients. In particular early transition into pressure support ventilation, even when patients violate conventional screening criteria for readiness-to-wean such as partial pressure of arterial oxygen to fraction of inspired oxygen ratio and positive end-expiratory pressure thresholds, neurological 'awakeness' and cardiovascular stability, has been shown to be safe and successful and increases the opportunity for patients to actively engage with rehabilitation [149].

Typically EM is characterised by a hierarchical progression of increasingly functional activities. Positioning and assessment of joint range of motion in sedated patients, progress to sitting over the edge of the bed, standing, marching on the spot and walking away from the bed-space in patients able to actively participate and engage with rehabilitation. Long-term patients can additionally be prescribed a bespoke exercise programme. These levels of exercise therapy have received international consensus on their definition by development of an agreed list of simple activity codes to facilitate accurate recording of patient treatment [150]. In addition to the aforementioned 'traditional' forms of EM, use of assistive technologies such as electrical muscle stimulation [151], passive cycle ergometry [152] and interactive video-game systems [153] can also be used to facilitate

prompt commencement of exercise. An extensive body of work has demonstrated the safety [154-158] and feasibility [137, 154, 159, 160] of EM interventions. Berney *et al* [155] reported no adverse event during delivery of EM in over 600 ICU exercise sessions. Furthermore clinical management algorithms based on consensus of expert opinion have been developed to facilitate decision-making of appropriate physical treatments to deliver depending on patient status e.g. unconscious, physiologically stable and deconditioned [161].

A number of randomised controlled trials have investigated the effect of a range of EM interventions. One of the earliest studies investigated a stepwise pulmonary rehabilitation-style programme in mechanically-ventilated patients with chronic obstructive pulmonary disease recovering from acute respiratory failure in a respiratory ICU. Nava [162] found that intervention group patients demonstrated significantly improved 6MWT distances (from time first able to mobilise to hospital discharge) ($p<0.0001$, exact values not reported). Maximum inspiratory pressure and visual analogue scale score for breathlessness were also significantly more improved in patients receiving the rehabilitation. Whilst these data are notable for their report well before the current interest in early mobilisation arose, it should be recognised that the patient cohort were prolonged ICU patients with less acuity, and the environment more akin to a long-term weaning unit than those that have been investigated more recently.

In 2009, Schweickert and colleagues compared standard care with an early physical and occupational therapy intervention comprising sedation interruption and progressive levels of physical and functional activity including transfers, bed mobility, standing and gait training commencing within 72hours of mechanical ventilation [163]. A greater percentage of patients receiving the intervention were found to return to independent functional status at hospital discharge (59% vs. 35%, $p=0.02$). In addition duration of mechanical ventilation (median (IQR) 3.4 (2.3-7.3)days vs. 6.1 (4.0-9.6)days, $p=0.02$) and number of ICU delirium days (2.0 (0.0-6.0)days vs. 4.0 (2.0-7.0)days, $p=0.03$) was also significantly better in the intervention arm. Ventilator-free days and Barthel score at hospital discharge approached statistical significance for difference between groups ($p=0.05$ for both outcomes). These findings, whilst demonstrating a positive effect from the EM

intervention, are limited in generalisability to ICU practice outside of the study country (North America) due to international differences in 'standard' ICU physiotherapy practice. Furthermore, strict sedation and weaning protocols were adhered to during the trial, which may not be in operation across all ICUs and which may have also influenced findings.

Burtin *et al* [164] studied the effect of bedside cycle ergometry for 20minutes per day in prolonged ICU stay patients. In this RCT, conducted in Europe, both groups received standard respiratory physiotherapy and passive or active upper and lower limb movements. At ICU discharge quadriceps force and physical function were not different between groups. However by hospital discharge 6MWT was significantly higher in the treatment group compared to the control group (median (IQR) 196 (126-329)m vs. 143 (37-226)m, $p<0.05$). Similarly the physical function domain of the SF-36 questionnaire was greater in those receiving the intervention (21 (18-23)points vs. 15 (14-23)points, $p<0.01$), as was improvement in quadriceps force from ICU to hospital discharge (1.83±0.91Nkg to 2.37±0.62Nkg, $p<0.01$ vs. 1.86±0.78Nkg to 2.03±0.75Nkg, $p=0.11$).

As the volume of published data examining EM in patients in the ICU has grown, a number of narrative [148, 165-168] and systematic [169-171] reviews have been undertaken collating and summarising findings. Whilst a variety of studies including case series and observational cohorts have been reported in the former publications, one of the latter reviews by Kayambu *et al* [169] additionally incorporated meta-analyses of data from eligible randomised controlled trial data, and thus represents the most robust form of evidence to determine the effects of EM in critically ill patients. Pooling findings from RCT and quasi-RCT studies, the authors concluded a significant positive effect favouring physical therapy for improving quality of life (Hedges g=0.4, 95%CI 0.08-0.71), physical function (g=0.46, 95%CI 0.13-0.78), peripheral muscle strength (g=0.27, 95%CI 0.02-0.52) and respiratory muscle strength (g=0.51, 95%CI 0.12-0.89). Length of hospital stay (g=-0.34, 95%CI -0.53- -0.15), length of ICU stay (g=-0.34, 95%CI -0.51- -0.18) showed significant reductions, and ventilator-free days increased (g=0.38, 95%CI 0.16-0.59). Interestingly, there was no effect on mortality observed. However exercise interventions were shown to vary considerably and further investigation

with larger sample sizes was advised to determine the mechanisms by which specific physical therapy strategies may demonstrate effect. The definition and clinically beneficial level, in terms of type, frequency and intensity of EM, currently remain undefined [148].

1.7.1.2 Ward-based physical rehabilitation

Far fewer studies have examined the effect of ward-based interventions for post ICU patients. Typically physiotherapeutic management of patients is directed towards hospital discharge planning, and the adequate level of mobility required for this to occur. Generic rehabilitation and support services may be available to patients including intermediate care, supported discharge and community therapy services but in the UK, as well as Europe, North America and Australia, these are for defined short periods of time with little scope for addressing more complex presentations, and rarely targeted specifically at post ICU patients. Furthermore, the level of mobility that reflects suitability for hospital discharge may not at all reflect premorbid function and this is not often accurately assessed in clinical practice.

A combined ward-based physiotherapy and nutritional rehabilitation package was evaluated by Salisbury *et al* [172] involving development of a unique generic rehabilitation assistant post [173]. This position was found to be a successful and valuable role for facilitating continuity of care for patients during the ICU-ward transition, and offering greater flexibility in the delivery of ward-based rehabilitation [173]. During the pilot phase of implementation of this post, a significant increase in the frequency of physiotherapy (median (IQR) 8.2 (7.1-10.6) vs. 2.6 (1.8-4.2)visits, $p<0.002$) and dietetic (4.9 (3.4-8.4) vs. 1.2 (0.6-2.1)visits, $p<0.001$) visits in intervention compared to control patients was evident [172]. This model of intervention is currently under investigation in a larger randomised controlled trial, with results pending [174, 175].

Interestingly Hopkins *et al* [176] found that of 65 patients who had received early mobility in their respiratory ICU, activity levels had decreased in 55% of patients on the first full ward day. Nearly twenty-five percent of patients who had walked

more than 100 feet at ICU discharge failed to mobilise at all on their first ward day, over one-third achieved less than their original distance, and only 41% demonstrated a comparable distance. These data highlight the importance of ensuring adequate delivery of rehabilitation therapy to patients to not only maintain but enhance performance. The role of a ward-based exercise therapy rehabilitation assistant could be wholly beneficial in the transition pathway from ICU to the ward, but further data are required.

Both Denehy *et al* [177] and Jones *et al* [178] have investigated the effectiveness of interventions conducted on the ward and that continued following hospital discharge. Denehy *et al* [177] utilised a bespoke exercise-based programme of up to one hour of cardiovascular, strength and functional activity, whereas Jones *et al* [178] developed a self-help rehabilitation manual. The primary end-point for Denehy *et al's* study was 6MWT distance at 12 months post ICU discharge, and whilst their intervention arm performed numerically better on the 6MWT at hospital discharge than those receiving usual care, the study was not powered to detect differences between groups following the ward-based period, nor were exploratory statistical analyses conducted to examine these data. The self-help rehabilitation manual adopted by Jones *et al* [178] was found to result in improved physical function at 8 weeks and 6 months post ICU discharge with a trend towards lower rates of depression, but again no outcome measures were evaluated following the ward-based period of intervention delivery to evaluate effect at this stage of the patient pathway.

1.7.1.3 Exercise-based rehabilitation following hospital discharge

Emerging data are appearing in the literature regarding effectiveness of exercise-based post hospital discharge rehabilitation interventions. Three recent randomised controlled trials have failed to show benefit, albeit this may be due to the methodology employed, the nature of the intervention and in particular, failure to stratify patients according to the presence of peripheral muscle weakness [177, 179, 180]. Furthermore, the lack of acknowledgement given to the standard level of rehabilitation and exercise therapy provided in usual practice would have reduced differences evident between control and intervention arms. Indeed,

control group patients received a standard level of rehabilitation within the ICU [177, 180] exceeding that delivered as the intervention in the previously described North American trial by Schweickert *et al* [163] which may have influenced subsequent patient ability at the later stage post hospital discharge.

However, recent pilot RCT data have demonstrated a significant improvement in 6MWT ($p<0.001$) and balance ($p<0.05$) as a result of cardiopulmonary exercise although these findings are preliminary, pending recruitment of the complete sample size, numerical values were not provided, and follow-up data beyond the immediate programme completion point have not been reported [181]. Further data also available in abstract form only, demonstrated no significant differences between groups for the primary outcomes of improvement in peak oxygen consumption (15.3% vs 17.7% for control and treatment respectively) and anaerobic threshold (16.2% vs 13.9%) following a seven week supervised exercise programme [182]. However greater improvements were observed in treatment patients compared to controls for SF-36 PCS (8.0 vs 4.1 points, $p=0.048$) and MCS (10.6 vs 4.0 points, $p=0.017$), and also peak power output (47.7% vs 20.4%, $p=0.024$).

A combined cognitive and physical intervention has shown greater improvements in patients in the intervention group for TUAG compared to control although these did not reach statistical significance (treatment effect -1.1, 95%CI (-4.1 to 2.0), $p=0.051$) [183]. In contrast to previous findings detailed above, balance scores did not differ between groups in this study at baseline or completion, albeit these were self-reported measures as opposed to results of objective assessment. However, little detail of the physical component of the intervention was reported by Jackson *et al* [183] in order to interpret these findings further.

Self-directed manuals have been investigated in two trials with contrasting results. Cuthbertson *et al* [184] demonstrated no significant improvement in physical (SF-36 PCS, mean (SD) 42.0 (10.6)points vs. 40.8 (11.9)points, effect size 1.1 (95%CI -1.9 to 4.2), $p=0.46$) or mental (SF-36 MCS, effect size 0.4 (-3.0 to 3.7), $p=0.83$) health-related quality of life, and furthermore that ICU follow-up was a more costly approach than standard care. In contrast, Jones *et al* [178] observed significant

improvements in SF-36 PF domain (p=0.006, raw values not reported) at 8 weeks and 6months following ICU discharge in intervention patients receiving a six-week rehabilitation manual incorporating physical, psychological and psychosocial advice. Ensuring robust strategies are in place to promote and monitor adherence to self-directed programmes are vital for their effective use, and this could have attributed to these differing findings.

Finally, in an uncontrolled observational cohort study of a six-session supervised cardiovascular training programme, significant improvements in exercise capacity (ISWT, from 278 (185-370) at baseline to 438 (370-510) at completion, p<0.001; 6MWT, from 180 (100-280) at baseline to 340 (250-450) at completion, p<0.001) and anxiety (baseline, 8.2 (5.0-11.0)points to completion, 6.2 (4.0-8.8)points, p=0.001) and depression (baseline 7.2 (5.3-9.0) to completion 4.4 (2.0-6.5), p=0.001). However the nature of study design employed by McWilliams *et al* [185] precludes determining the true effect of the intervention.

A previous integrative review of post hospital discharge rehabilitation programmes for survivors of critical illness highlighted the variability in structure, content, type and format of delivery of physical interventions employed in trials [186]. This review included both published data available at the time, and trial registry and protocol sources of information in order to examine as wide a range of evidence to explore the characteristics of physical treatments under investigation. Building on the findings of that review, Table 1-3 and Table 1-4 present a comprehensive update on the current evidence base for studies investigating physical rehabilitation interventions delivered following hospital discharge in survivors of critical illness. A number of important factors related to features of exercise-based post hospital discharge rehabilitation interventions are highlighted.

Timing of intervention delivery

In the chronic obstructive pulmonary disease patient population, early pulmonary rehabilitation delivered one week following acute exacerbation is both safe and effective, with fewer hospital attendances [187] and improvements in exercise capacity and health status [188] observed. Adopting a similar approach for the

post critical illness population would seem appropriate. In those studies where the time-frame for commencing post hospital discharge interventions are specified, this ranges from one week [180], two weeks [177, 189] and up to four months [179]. In many cases the rehabilitation programme commences during the in-patient stay [177, 178, 184, 190], representing a seamless continuation of the programme at the post hospital discharge stage. In addition this has the potential to maximise benefit and adherence if patients are familiar and already engaged with the rehabilitation process, and the staff involved. A protracted delay in baseline assessment and initiation of post hospital discharge exercise interventions could reduce any potential effect size from natural recovery occurring in the interim period. Trials investigating interventions at this stage of the patient pathway should accurately monitor the trajectory of recovery from the point of hospital discharge up until the intervention is commenced. This, in combination with a control arm, will facilitate determining the real effect of any intervention and the optimum time-frame for delivery.

Exercise prescription

Variability in detail reported by studies limits this area and a range of exercise components are included. Cardiovascular aerobic exercise is the most commonly reported feature of post hospital discharge exercise-based rehabilitation programmes [177, 179, 180, 185, 189, 191, 192] including activities such as treadmill walking, ground walking and cycling. Initial exercise prescription is based on results of walking tests or cycle ergometry, and target exercise intensities incorporate use of perceived rate of exertion scales or physiological parameters such as heart rate reserve or oxygen consumption. The Borg score, aiming to achieve levels of moderate exertion, is commonly utilised [177, 179, 180, 185, 189], although it has not been demonstrated that this level of exertion confers benefit to physical, functional or health-related quality of life outcomes. For those studies that include unsupervised exercise sessions, use of measures such as the Borg score and heart rate can be taught to patients to ensure this exercise is both safe and at a suitable level of intensity. Progression of cardiovascular exercise is based on reassessment of similar measures, although as patients progress in ability, use of functional tests could also be of value.

Strength exercises are included in a number of programmes, commonly using the repetition maximum principle to guide initial prescription and subsequent progression of weights used [177, 180, 189, 191]. Where functional activities are employed, [177, 183, 189], such as sit-to-stand or transfers, it is important that these are standardised and clearly described to ensure objectivity and reproducibility with regard interpreting their potential effect.

Structure and format

Supervised, hospital-based, outpatient programmes are the most common style of rehabilitation programme. Sessions vary between once and twice-weekly, ranging 40-60minutes of exercise, with programmes typically between six to eight weeks duration (Table 1-3). Supervising exercise sessions allows clinicians to ensure patients are exercising safely and correctly, and that exercises can be progressed as soon as necessary. In addition some patients may benefit from the psychological support of peers. Data from the field of pulmonary rehabilitation suggests enhanced clinical and patient-centred outcomes as a result of supervised sessions [193]. However such a format may not be feasible for those patients whose geographical area of residency precludes repeated visits to the hospital, or for those who prefer not to exercise in a group setting. Nonetheless unsupervised home-based programmes rely wholly on patient engagement and motivation for adherence, and reliance on them to correctly learn and carry out the specific exercises. An in-depth and detailed training package would therefore be a prerequisite, as well as regular telephone contact to review patient progress and manage any queries arising throughout the programme. It is acknowledged that documentation in home exercise diaries can be variable, and therefore use of pedometers or accelerometers could be used to supplement these records, and provide structured and objective feedback for patients regarding levels of exercise.

Evaluation of intervention effectiveness

There is currently no consensus on which outcomes should be used to evaluate effectiveness of exercise-based rehabilitation programmes at any stage of the patient pathway. Studies investigating the post hospital discharge stage of

recovery utilise a range of physiological, clinical, patient and healthcare utilisation outcomes, with outcome measures including oxygen consumption and anaerobic threshold, exercise capacity, physical and mental health-related quality of life, physical activity, return to work and cost effectiveness (Table 1-4). In the future, development of a core set of outcomes for evaluation of interventional trials of post critical illness rehabilitation would facilitate protocol standardisation and comparison of results.

The current state of the evidence base for post hospital discharge rehabilitation for survivors of critical illness highlights the lack of conclusive data on the optimum timing, dose and format of delivery of such interventions. Acknowledgment that patients continue to experience physical functional deficits for up to five years following the index critical illness [105], highlights the need for a longitudinal approach to the management of post critical illness disability [194]. Future research must focus on post hospital discharge exercise therapy and rehabilitation interventions that are delivered at various time points following hospital discharge according to the trajectory of recovery of the individual patient [130], as this approach could demonstrate enhanced benefit by addressing the heterogeneity of this patient population.

Table 1-3 Study design, and intervention and control group description of post hospital discharge rehabilitation programmes

Study	Design/sample	Intervention group			Control group
		Structure/format	**Exercise component**	**Participant contact**	
Batterham *et al*, 2014 [179, 195] *Published data and trial registration*	Multi-centre, parallel group, RCT n=59	Hospital outpatient-based, commencing 8-16weeks post hospital discharge 40minutes, twice-weekly for 8weeks	Aerobic exercise (cycle ergometry) Exercise intensity target level 12-14 on the 20point Borg scale of perceived exertion (moderate intensity) Unsupervised home programme (x1/week 40minutes brisk walk)	Minimum 2 supervised sessions per week at outpatient classes	Usual care
Denehy *et al*, 2013* [177, 196] *Published data and protocol*	Single-centre, stratified, assessor-blinded RCT n=150	Hospital outpatient and home-based, commencing within 2weeks post hospital discharge 60minutes, twice weekly for 8weeks Completion defined as attending >70% (>11 sessions) of the 16 available	Individualised exercise programme with cardiovascular, progressive resistance strength training and functional exercise; unsupervised home walking programme once weekly Prescribed from pre-outpatient 6MWT, cycle ergometer, 5RM Intensity of 4-6 on modified Borg Scale, and commenced at 70% peak walking speed	Minimum 2 supervised sessions per week at outpatient classes	Usual care (no outpatient exercise classes) Transfer to rehabilitation facility if deemed necessary by ward physiotherapist involved in discharge planning

Battle *et al*, 2013 [181, 191] *Published data in abstract form, and trial registration*	Single-centre, pragmatic, blinded RCT Target=60	Hospital outpatient-based Up to 60minutes, twice-weekly for 6weeks	Cardiovascular (treadmill, cycle ergometer, rowing machine, stepper), balance and strengthening exercises	Minimum 2 supervised sessions per week at outpatient classes	No treatment
Connolly *et al*, 2013 [189, 197] *Published data in abstract form, and trial registration*	Dual-centre, pilot feasibility RCT n=20	Hospital outpatient-based commencing within two weeks of hospital discharge Up to 40mins, twice-weekly for 16 sessions	Cardiovascular (treadmill, static cycle, walking), strength, balance and function; unsupervised home exercise programme once weekly	Minimum 2 supervised sessions per week at outpatient classes	Once weekly telephone call
McWilliams *et al*, 2013 [182] *Published data in abstract form*	Single-centre RCT n=63	Hospital outpatient-based Seven week exercise and education programme	*Not detailed*	*Not detailed*	No intervention
Jackson *et al*, 2012 [183] *Published data in full*	Single-centre, feasibility, pilot RCT n=21	Home-based Multi-modal cognitive, physical and functional rehabilitation for 12weeks	Lower extremity function and endurance (e.g. chair stands, toe rises, stair-climbing, walking) Progressively increased according to patient ability Exercise prescriptions individually tailored according to functional status Unsupervised independent home exercise programme	12 visits, six face-to-face, six utilising telehealth; each lasting 60-75minutes	Usual care rehabilitation-related interventions after hospital discharge as determined by medical team

Elliott *et al*, 2011 [180, 198] *Published data in full, and protocol*	Multi-centre, assessor-blinded RCT n=195	Home-based commencing 1 week post hospital discharge 20-30 minutes, up to 5 sessions/week unsupervised, for 8 weeks	Graded, individualised programme of walking, upper and lower limb strengthening, core stabilisation, flexibility and stretches Exercise manual accompanied exercise advice, focus on endurance and strength training Exercise intensity determined using 6MWT distance and Borg score; exercise prescription based on results of 6MWT, 8RM	3 home visits with supervised sessions 60-90 minutes, and 5 phone-call follow-ups	Usual community-based care e.g. visits to general practitioner
O'Neill *et al*, 2011 [192] *Trial registration only*	Multi-centre, single-blinded RCT Target=68	Hospital, outpatient-based Twice-weekly for 6weeks	Aerobic exercise Unsupervised independent home exercise programme accompanied by a written exercise manual	Minimum 2 supervised sessions per week at outpatient classes	Standard care
Griffiths *et al*, 2010* *Trial registration only*	Multi-centre, single-blinded RCT Target=180	Hospital, outpatient-based, commencing in hospital on the ward 60minutes, once-weekly, duration of programme dependent on hospital LOS	Not specified Two unsupervised home exercise sessions	Minimum 1 supervised session per week at outpatient class	Four-arm trial investigating combinations of a dietary supplement, enhanced PT programme, ICU recovery manual and placebo nutritional supplement
Cuthbertson *et al*, 2009 [184, 199]	Multi-centre, non-blinded RCT	Nurse-led ICU follow-up programme commencing	Not specified	Clinic appointments at 3m and 9m	No intensive care follow-up after hospital

Published data in full, and protocol	n=286	in hospital on the ward Three month programme	Individualised, self-directed following review by physiotherapist		discharge
McWilliams *et al*, 2009 [185] *Published data in full*	Non-randomised, uncontrolled n=38	Hospital, outpatient-based, commencing up to 3 weeks post hospital discharge Up to 20mins, once weekly for six weeks Exercise and education (1hr session)	Cardiovascular exercise involving all major muscle groups with periods of active recovery Four different exercise intensity levels determined by varying ration of exercise to active recovery, to achieve target Borg scores (3-4) and heart rate reserve (50-60% for high risk patients, 60-70% for low risk patients) Two unsupervised home exercise sessions	Minimum of one supervised session per week at outpatient class	*Not applicable*
Jones *et al,* 2003* [178] *Published data in full*	Multi-centre, assessor-blinded RCT n=126	Home-based 6week rehabilitation manual incorporating physical, psychological and psychosocial advice; duration of programme dependent on hospital LOS	Unsupervised, self-directed Individually tailored to patients	Three phone calls during intervention period	Routine ICU follow-up (contact by telephone on three occasions post hospital discharge, and 2 attendances at dedicated ICU follow-up clinic at 8weeks and 6m)

*Study involves rehabilitation intervention commencing prior to hospital discharge. Only information relevant to post hospital discharge stage of delivery presented.

Abbreviations: RCT = randomised controlled trial. 6MWT = Six Minute Walk Test. RM = repetition maximum. LOS = length of stay. PT = physiotherapy. ICU = intensive care unit.

Table 1-4 Outcome measure, assessment and results of post hospital discharge rehabilitation programmes

Study	Outcomes/outcome measures	Assessments	Results
Batterham *et al*, 2014 *Published data and trial registration*	Fitness – anaerobic threshold, mlO_2/kg/minute (primary) Quality of life – SF-36, EQ-5D (primary) Time to return to work Mental health – HADS Habitual physical activity	Baseline, week 9, and at 26weeks	n=59 Small benefit from the intervention for AT of 1.8 (95%CI 0.4-3.2)mlO_2/kg/min at week 9, not sustained at week 26. Possible beneficial effect on SF-36 physical function (3.4, (95%CI -1.4 to 8.2)points) domain at week 9, and mental health domain at week 26 (4.4 (95%CI -2.4 to 11.2)points)
Denehy *et al*, 2013* [177, 196] *Published data in full, and protocol*	Physical function – 6MWT (primary) TUAG, PFIT Patient-reported – SF-36, AQoL	Baseline, ICU discharge, 3m, 6m, 12m post ICU discharge	No significant difference between groups at hospital discharge, 3m, 6m, and 12m post ICU discharge, for 6MWT, TUAG, or PFIT. Rate of change over time and mean between-group differences in 6MWT from first assessment greater in the intervention group up to 3m No between-group differences in AQoL or SF-36 v2 domains at any time point
Battle *et al*, 2013 [181, 191] *Published data in abstract form, and trial registration*	Cardiopulmonary fitness – 6MWT (primary) Balance – Berg Balance Score Grip strength – handgrip dynamometry Anxiety and depression - HADS	Baseline, 7 weeks, 6m and 1 year	Preliminary results; significantly greater improvements in cardiopulmonary fitness ($p<0.001$) and balance ($p<0.05$) in the exercise group (n=10) compared to control (n=10) at 7weeks; Numerically, but not statistically significant, greater improvements in anxiety, depression and grip strength
Connolly *et al*, 2013 [189, 197] *Published data in abstract form, and trial registration*	Exercise capacity – ISWT, 6MWT HRQL – SF-36, HADS Physical function – TUAG, STS-5, Barthel scale Peripheral skeletal muscle mass and size, anthropometrics	Baseline (hospital discharge), completion (3months post hospital discharge)	No significant difference between control and intervention for any outcome; both groups demonstrating improvements beyond minimum clinically important difference

McWilliams *et al*, 2013 [182] *Published data in abstract form*	CPET – peak oxygen consumption (VO_2) and anaerobic threshold (primary) HRQL – SF-36 CPET – other parameters	Hospital discharge (24±13days) and at 8-10weeks	No significant difference between groups in improvements in peak VO_2 (15.3% vs 17.7% for control and treatment) and anaerobic threshold (16.2% vs 13.9%); significantly greater improvements in treatment than control groups for SF-36 PCS (8.0 vs 4.1, p=0.048), and MCS (10.6 vs 4.0, p=0.017) Improved peak power output also evident in treatment vs control groups (47.7% vs 20.4%, p=0.024)
Jackson *et al*, 2012[#] [183] *Published data in full*	Cognitive function – TOWER (primary) Physical function – TUAG (primary) Cognition – MMSE, DQ Physical function – ABC scale Daily function – FAQ, Katz ADL Scale	Hospital discharge (baseline) and 3m	Greater improvement in intervention group for TUAG compared to control, although non-significant. Self-efficacy scores of ABC did not differ between groups
Elliott *et al*, 2011 [180, 198] *Published data in full, and protocol*	Physical function – SF-36 PF domain HRQL – SF-36 other components Exercise capacity – 6MWT	Baseline (one week post hospital discharge), 8 weeks and 26weeks	Both control and intervention groups demonstrated significant and clinically important improvements in SF-36 v2 PF scores and 6MWT distance at 8weeks, which continued to 26weeks. No significant group effects or group by time interactions.
O'Neill *et al*, 2011 [192] *Trial registration only*	Physical function – SF-36 PF domain (primary) Physical function – RMI Hand function – handgrip dynamometry, NHPT Exercise capacity – ISWT HRQL – FLP, SF-36, HADS Self-efficacy – 'Readiness to change' questionnaire, CDSE Scale, EQ-5D Breathlessness – MRC Dyspnoea Healthcare utilisation	Baseline and 6weeks	*Not available*

Griffiths *et al*, 2010* [190] *Trial registration only*	Exercise capacity – 6MWT (primary, at 3m) Insulin resistance – improved levels (at 1yr) HRQL – *not specified* (at 1yr)) Muscle mass and bone density – DEXA scanning (at 1yr)	Baseline, 3m and 1yr	*Not available*
Cuthbertson *et al*, 2009 [184, 199] *Published data in full, and protocol*	HRQL – SF-36 PCS and MCS (at 12m, primary) HRQL – SF-36 (at 6m) QALYs – EQ-5D PTSD symptoms – DTS Anxiety and depression – HADS Healthcare utilisation and patient satisfaction	Baseline, 6m and 12m	No significant difference in SF-36 PCS or MCS, or any secondary outcomes, between control and intervention groups at 12m. Intervention significantly more costly
McWilliams *et al*, 2009 [185] *Published data in full*	Exercise capacity – ISWT and 6MWT (primary) Anxiety and depression - HADS	One week pre- and post-intervention	Significant improvements in exercise capacity (ISWT median change 160m, p<0.001, 6MWT median 160m, p<0.001) and anxiety and depression (p=0.001)
Jones *et al*, 2003* [178] *Published data in full*	Depression and anxiety – HADS Phobic symptoms – Fear Index PTSD symptoms – Impacts of Events Scale HRQL – SF-36 physical function	Baseline, 8weeks and 6m post ICU discharge	Significant improvements in SF-36 physical function in intervention group compared to control at 8weeks and 6m (p=0.006), with a trend towards lower rates of depression at 8weeks (12% vs. 25%) No difference between groups in anxiety or PTSD symptoms

*Study involves rehabilitation intervention commencing prior to hospital discharge. Only information relevant to post hospital discharge stage of delivery presented. #Data for physical function only presented.

Abbreviations: 6MWT = Six Minute Walk Test. TUAG = Timed Up And Go. PFIT = Physical Function in ICU Test. SF-36 = Short-Form 36 v2 questionnaire. AQoL = Assessment of Quality of Life. ICU = intensive care unit. HADS =Hospital Anxiety and Depression Scale. ISWT = Incremental Shuttle Walk Test. HRQL = health-related quality of life. STS-5 = Sit to Stand x5. EQ-5D = European Quality of Life-5Dimensions. CPET = cardiopulmonary exercise testing. PCS = Physical Component Score. MCS = Mental Component Score. TOWER = Delis-Kaplan Tower Test. MMSE = mini-mental state evaluation. DQ = Dysexecutive questionnaire. ABC = Activities Balance and Confidence scale. FAQ = Functional Activities Questionnaire. ADL = Activities of Daily Living. PF = Physical Function. RMI = Rivermead Mobility Index. NHPT = Nine Hole Peg Test. FLP = Functional Limitations Profile. CDSE = Chronic Disease Self-Efficacy scale. MRC = Medical Research Council. DEXA = dual energy x-ray absorptiometry. QALYs = quality adjusted life years. PTSD = post traumatic stress disorder. DTS = Davidson trauma score.

1.7.2 NICE Clinical Guideline CG83

In 2009, the National Institute for Health and Care Excellence (NICE) published clinical guideline NICE CG83, 'Rehabilitation after critical illness' [136]. This document represented a significant landmark in the management of survivors of critical illness with ongoing impairment and disability, and served to promote the clinical and research agenda surrounding rehabilitation for post ICU patients. NICE CG83 outlined three stages of the patient pathway where rehabilitation was advocated for delivery in a structured and coordinated fashion by a multidisciplinary team. Following comprehensive clinical assessment and identification of those patients 'at risk', rehabilitation commences in the ICU and continues following transfer to the ward and post hospital discharge. The transition between stages should be marked by a seamless handover between clinicians responsible for patient management in the different environments, including verbal and documented summaries of progress to that stage and reappraisal of patient ability and individual goals. Ideally a keyworker facilitates this process. Specifically at the stage of hospital discharge, it is recommended that patients undergo a functional assessment of physical and non-physical dimensions and the impact on activities of daily living. Ongoing rehabilitation needs are identified with referral into necessary follow-up and/or rehabilitation services. Following hospital discharge, at the 2-3month period, a review of the patient should re-evaluate progress against the earlier functional assessment and if recovery is suboptimal or there is evidence of new impairment, further referrals to rehabilitation services are advised.

However, one significant limitation to NICE CG83 has been the lack of substantial evidence supporting physical interventions, or describing detail of optimal rehabilitation programmes to address impairment and outcome measures to use for evaluation. For clinicians working with post critical illness patients on a daily basis, the 'Who, What, Where, When and How' questions required to clearly identify changes in practice remained unanswered. Consequently, wider uptake and application of the guidelines in a standardised and comprehensive approach have been limited and inconsistent across different regions and even individual organisations.

Two UK surveys have been conducted gauging adherence to NICE CG83. In 2011, Appleton *et al* [200] targeted lead medical and physiotherapy clinicians at all ICUs across Scotland achieving a near complete response rate across both professions using a telephone survey. Of these, only a minority had actually read the guidelines (14% and 30%, respectively), and of those that had only two-thirds considered them a useful document. The authors found that few of the recommendations from NICE CG83 were being adopted in Scottish ICUs, notably a consistent approach to the assessment of physical and psychological morbidity, delivery of active physical rehabilitation strategies whilst patients are in the ICU, and limited provision of assessment or therapy to address ongoing impairment beyond ICU discharge. However, this survey lacks generalisablity of findings through data acquisition in one region only, and furthermore content of the survey emphasised practice within the ICU with little examination of ward-based or post hospital discharge stages of care.

More recently, Berry *et al* [201] systematically examined all recommendations from NICE CG83. Questionnaires were distributed across a number of UK critical care networks and completed by ICU nursing staff. Greatest adherence to recommended practice was evident during the ICU stay, with just over half of all units surveyed compliant with implementation. However further examination of individual components revealed that the lowest level of uptake related to comprehensive clinical patient assessment and goal-setting. From ICU discharge onwards, levels of adherence overall declined with the lowest evident at the post hospital discharge. Often the recommendations in greatest effect were those regarding information-giving, either during handover of care between clinicians or involving communication with families. Least operational were recommendations that related to the actual delivery of rehabilitation interventions. Notably at all stages, a proportion of respondents indicated that they had no action plan in place to address non-compliance. Whilst causes for this were not specifically explored, one potential reason could be the lack of usefulness of the guidelines reported by Appleton *et al* [200]. Only one third of respondents indicated review and functional reassessment for patients at 2-3months post hospital discharge with few follow-up services available, which were mainly nurse-led, not formally commissioned or evaluated, and funded mainly from ICU budgets.

Whilst offering a comprehensive review of the individual recommendations pertaining to each stage of the patient pathway, there are also limitations to this survey. Data collection was significantly restricted, with a 60% response rate from an overall cohort of ICUs that excluded key regional areas. Missing data further limited analyses, and it was not clear whether respondents were in clinical roles that would give them sufficient insight to respond appropriately.

Nonetheless, these two surveys highlight the inconsistent application of NICE CG83 in the clinical setting, particularly at the post hospital stage. However, a more comprehensive survey of practice across the UK may provide a more accurate picture of NICE CG83 guideline implementation. Furthermore, given the low adherence reported to date, a more detailed exploration of the barriers that exist to service provision would also provide valuable data for considering strategies to optimise wider adherence. With regard to the delivery of exercise-based interventions to address physical functional deficits, detailed surveys targeted at relevant members of the multidisciplinary team who are able to provide the most accurate responses would be a wholly rationale approach.

1.8 Summary

This comprehensive literature review has summarised the background behind the studies undertaken in this thesis. There are limitations to the current forms of volitional manual muscle testing used to assess ICU-AW, in particular the MRC-SS, and as a clinical diagnostic tool there are currently no data reporting test characteristics in terms of inter-rater reliability and clinical outcome, which are essential facets of this test that must be investigated. However, ultrasound is a useful non-volitional technique that is developing an increased profile for assessing a variety of peripheral skeletal muscle architecture parameters, and for which there is evidence for its use in monitoring the trajectory of muscle wasting during critical illness. Despite this, further work comparing the anatomical and physiological cross-sectional area of rectus femoris is required and indeed required to confirm its relationship with peripheral skeletal muscle force which would validate its use a surrogate measure. Exercise-based rehabilitation has been advocated to address the ongoing physical functional impairment resulting from

ICU-AW throughout the patient pathway from ICU admission to hospital discharge and beyond. Specifically, hospital discharge marks the transition of clinical management from hospital to the community at which point follow-up of post critical care patients and rehabilitation for such patients may become more inconsistent with limited available services. There are limited data that have investigated the barriers to delivery of rehabilitation at this stage and little is known of the optimum structure of a post hospital discharge exercise-based rehabilitation programmes. Establishing an evidence-base for an exercise and rehabilitation intervention at this stage of recovery would be beneficial for not only enhancing patient management but also would be clinically useful in informing specialist national guidance.

1.9 Aims of thesis

The overarching research framework of this thesis was to (1) investigate the clinical predictive value of peripheral skeletal muscle weakness in critically ill patients within the ICU measured with volitional techniques (2) establish the clinical validity of measuring physiological rectus femoris cross-sectional area (3) investigate the clinical usefulness of ultrasound as a non-invasive method to assess muscle wasting (4) investigate the effect exercise-based rehabilitation following critical illness on clinical outcome and (5) determine the barriers to delivery of exercise-based rehabilitation in the post hospital discharge stage of recovery. This work has been based on the relationship between peripheral skeletal muscle wasting and weakness that occurs as a consequence of critical illness and the goal to promote physical activity to enhance skeletal muscle function by embedding exercise-based rehabilitation into the recovery processes of the patient (Figure 1-4).

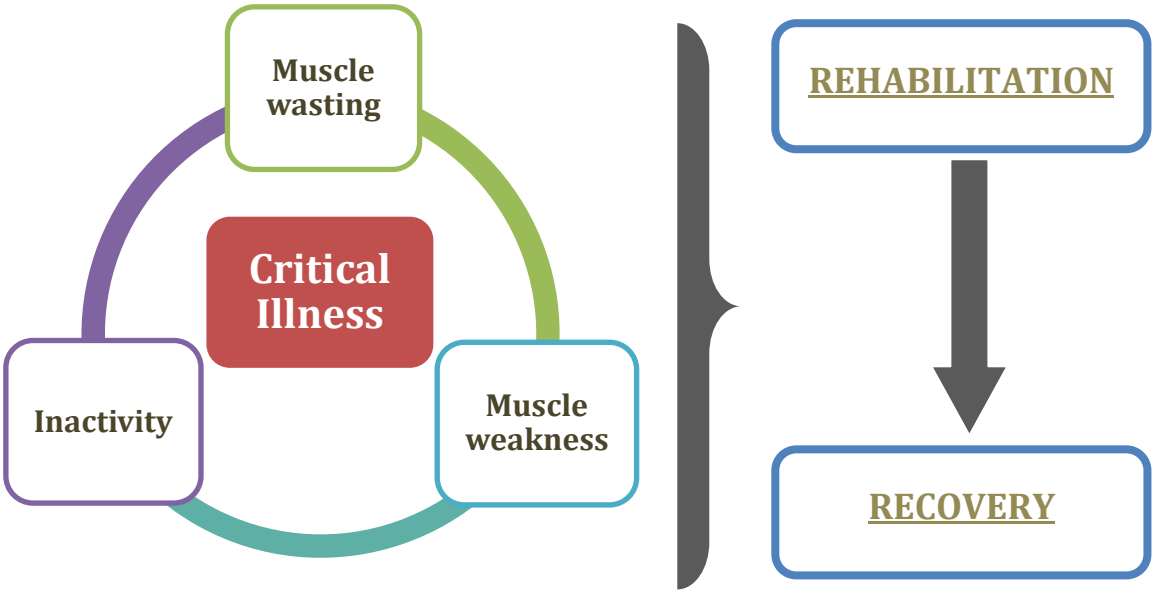


Figure 1-4 Overarching research framework

Study One (*Chapter 3*) aimed to (1) determine inter-observer agreement for the Medical Research Council-Sum Score for critically ill patients whilst in the ICU, against simulated weakness presentations and (2) investigate the clinical predictive value of Medical Research Council sum-score in critically ill patients whilst in the ICU.

Study Two (*Chapters 4 and 5*) aimed to establish the clinical validity of measuring physiological rectus femoris cross-sectional area as a marker of muscle force production as well as assessing the clinical usefulness of ultrasound in the assessment of peripheral skeletal muscle architecture during critical illness.

Study Three (*Chapter 6*) investigated the effect of exercise-based rehabilitation following hospital discharge in survivors of critical illness with ICU-AW. Embedded in this study was an observational cohort study to assess the trajectory of recovery in patients without ICU-AW.

Study Four (*Chapter 7*) aimed to determine the prevalence, delivery and barriers to establishing post hospital discharge follow-up and rehabilitation services across the United Kingdom.

Chapter 2 Methods

2.1 Ethical approval

The studies reported in this thesis were approved by London Westminster Research Ethics Committee (formerly St.Thomas' Hospital Research Ethics Committee), REC study code 09/H0802/80. Site-specific approval for the studies to be performed was granted by the Research & Development Departments of St.Thomas' Hospital, London (study registration code RJ1 09/N153) and King's College Hospital, London (study registration code KCH 1412). All participants gave written informed consent prior to participation in the studies detailed.

2.2 Participants

Post critical illness patients involved in these studies were recruited from the General Intensive Care Units and High Dependency Units of St.Thomas' Hospital, and King's College Hospital, London. Healthy subjects were recruited from hospital and research staff at both sites, their relatives, and from a registered bank of healthy volunteers with prior experience of participating in clinical studies at both sites. All participants received information leaflets regarding the relevant study to read thoroughly prior to consenting. A copy of the consent form was given to all participants.

2.3 Assessment of intensive care unit-acquired weakness

Intensive care unit-acquired weakness (ICU-AW) was assessed using the Medical Research Council sum-score (MRC-SS) [35]. A measure of global peripheral skeletal muscle strength, six functional upper and lower limb muscle groups are assessed bilaterally using the MRC scale ranging from 0 (no contraction) to 5 (normal power) [34] (Table 2-1). Total scores range from 0 (paralysis) to 60 (complete/normal strength). Measurements were performed in either supine or seated positions, following a standardised protocol for each assessment position (*Appendix I*). An MRC-SS of less than 48 out of 60 was considered diagnostic of ICU-AW, as previously reported [5].

Table 2-1 Medical Research Council sum-score

Muscle Groups Assessed	Medical Research Council Strength Grade
Shoulder abduction	0 – no visible contraction
Elbow flexion	1 – visible contraction but no limb movement
Wrist extension	2 – active movement with gravity eliminated
Hip flexion	3 – active movement against gravity
Knee extension	4 – active movement against gravity and resistance
Ankle dorsiflexion	5 – active movement against full resistance/normal power

2.4 Measures of exercise capacity

The gold standard measurement of exercise capacity typically involves use of laboratory-based incremental tests e.g. cycle or treadmill ergometry to achieve maximum performance [202]. However, in the clinical context of rehabilitation programmes, where access to equipment and resources may be more limited, simple field-based exercise tests such as the Incremental Shuttle Walk Test (ISWT) and Six Minute Walk Test (6MWT) can be used to assess exercise capacity [203, 204].

2.4.1 Incremental Shuttle Walk Test

The ISWT is an externally-paced exercise test during which subjects achieve a symptom-limited maximum performance [205] allowing objective measurement of exercise capacity. Standardised, pre-recorded instructions are given (Glenfield Hospital, Leicester, UK). Subjects walk up and down a 10m course (shuttle), located in a quiet, flat area and marked out by two cones inset 0.5m from the end of each shuttle (Figure 2-1).

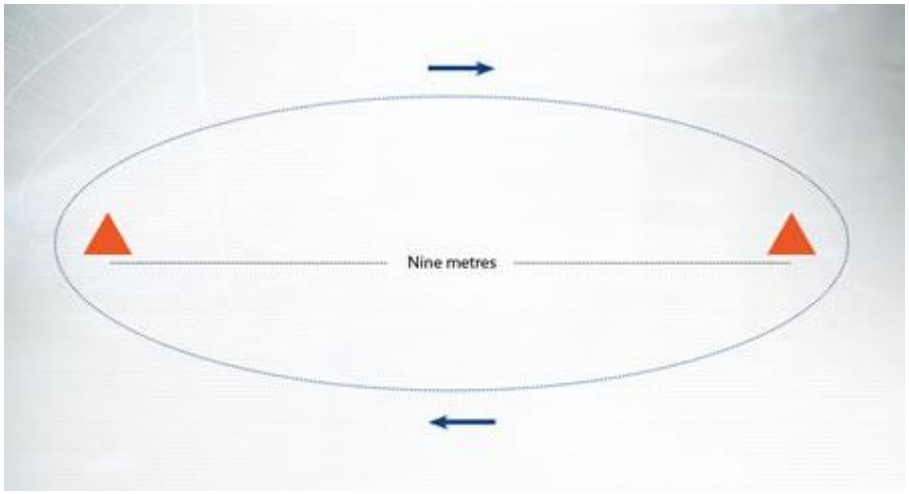


Figure 2-1 Outline of Incremental Shuttle Walk Test course

Reproduced with permission from Alison J et al, The Pulmonary Rehabilitation Toolkit on behalf of The Australian Lung Foundation (2009) [206])

Walking pace is dictated by a pre-set audio signal on a pre-recorded disc (Glenfield Hospital, Leicester, UK) played on a conventional CD player. As the test progresses through each level, beep signals quicken requiring the subject to walk at progressively quicker speeds to reach the end of each shuttle in time. There are twelve levels in total, with an increasing number of shuttles to complete in each. Initial walking speed for Level 1 is 0.5m/s increasing by 0.17m/s at each level. Subjects completing a shuttle prior to the beep signal were instructed to wait until the beep signalled again before proceeding with the next shuttle. Standardised pre-test advice and verbal prompts were given to increase speed if the subject was more than 0.5m away from the cone when the beep sounded, and to increase walking pace slightly at the start of each new level. Number of shuttles completed by each subject was totalled. Use of mobility aids and supplemental oxygen were recorded.

Blood pressure was measured prior to commencing the test. Fingertip heart rate (HR) and oxygen saturation (SpO_2) were recorded prior to and during the test using a pulse oximeter (Nonin Onyx®9500 Fingertip Pulse Oximeter™, Nonin Medical Inc, Plymouth, MN, USA). This is a small, lightweight, portable, commercially available device, accurate in measuring SpO_2 (range 70-100%) and HR (range 20-250bpm) in accordance with International Organisation for Standardisation guidelines (ISO 9919:2005, Standard Specification for Pulse

Oximeters for Accuracy) (Nonin Onyx®9500 Instructions for Use, ©2006), and which meets international standards for measurement of pulse oximetry during exercise testing [202].

Breathlessness was quantified prior to and on completion of the test using the Modified Borg scale (MBS) and a visual analogue scale (VAS). The MBS is based on an original scale rating perceived exertion developed by Borg [207] and is a reliable and valid tool for measuring breathlessness in respiratory disease [208]. Subjects are asked to rate their perceived levels of breathlessness on a scale ranging from a minimum of 0 (no breathlessness) to 10 (maximal breathlessness). These same two reference points were used on a VAS to rate subjects' perceived levels of breathlessness. Symptoms of leg fatigue were similarly assessed using the MBS and a VAS, with 0 indicating no leg fatigue, discomfort or tiredness and 10 being the maximum experience of these symptoms.

Termination of the ISWT occurred if the subject completed all shuttles at each level of the test, or conversely became unable to maintain the required pace necessary to complete each shuttle (reflected in a reaching a distance more than 0.5m away from the cone when the beep signalled) [205]. The test could also be terminated by the subject if they became too breathless to continue, and/or the investigator if cardiopulmonary or other systemic symptoms manifested e.g. 85% maximum heart rate achieved, persistent desaturation [205, 206]. At the end of the test SpO_2 and HR were monitored during a two minute recovery period, and total number of shuttles completed was recorded.

An initial practice test was undertaken at baseline for familiarisation purposes and to account for a learning effect. Tests were separated by a minimum of 30minutes, and the best result of the two was recorded [206]. A minimum clinically important difference (MCID) for the ISWT has been reported as 47.5m [209], albeit derived from patients with chronic obstructive pulmonary disease, and the test is valid as a measure of functional capacity, correlating strongly with performance during a maximal treadmill exercise test [210].

2.4.2 Six Minute Walking Test

The Six Minute Walking Test (6MWT) is a self-paced, sub-maximal walking test [211, 212]. Subjects mobilise as far as possible at their own pace, for six minutes along a pre-determined 10m course (marked out with two cones each inset 0.5m from each end) without running or jogging. Standardised pre-test instruction is given and subjects are informed as each minute of the test passes [212].

Breathlessness and leg fatigue were measured prior to and on completion of the test using Borg and VAS scores as previously described. Blood pressure was measured at the beginning of the test. HR and SpO_2 were measured at the start of the test, at each minute interval during the test, and on completion using a pulse oximeter (as per the ISWT). Rest periods during the six minute period are allowed and recorded. The test concludes at the end of six minutes. However, as with the ISWT, the test can be terminated at an earlier time by either the subject or the investigator with reasons for early termination noted. Total distance walked at the end of six minutes was calculated. Use of mobility aids and supplemental oxygen were permitted and documented. Previous reports have identified an MCID for the 6MWT as 54m [213]. Recently this has reduced to 35m [214], and 25m [215].

2.4.3 Difference between ISWT and 6MWT

Whilst the ISWT can replicate maximal performance that may potentially be achieved under laboratory conditions [210], as a self-paced, sub-maximal field test the 6MWT can be considered useful for measuring functional walking capacity that may be evident during the course of daily activity [211]. Predicted 6MWT distances for healthy adults can be calculated from reference equations [216, 217], and a distance of <350m has been shown to be predictive of mortality in the chronic respiratory disease population [218].

2.5 Measures of health-related quality of life

2.5.1 Short-Form 36 version 2 questionnaire

The Short-Form 36 version 2 questionnaire (SF-36) surveys multiple aspects of health-related quality of life (HRQL) [219] (*Appendix II*). Individual items incorporated in questions are collapsed down into eight scales or domains (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, Mental Health) which are further summarised in two component measures of Physical and Mental Component Scores [219]. The questionnaire is either self-completed by patients or administered by the researcher. Higher scores indicate greater levels of quality of life. In the studies reported in this thesis, the 'Acute Recall' version of the SF-36 questionnaire was employed. In this version, the symptom recall period respondents are asked to consider is reduced to one week, compared to four weeks adopted in the 'Standard' version of the tool. The rationale for this recall period is an enhanced sensitivity to recent changes in health status [220], and which was therefore considered more applicable to the acute post critical illness patient population.

The SF-36 has been used widely in differing patient groups, and normal values for age, gender and a number chronic diseases have been determined [219, 221]. In the ICU population, the SF-36 has been shown to be an acceptable tool for measuring HRQL, demonstrating reliability, content validity, and responsiveness to change [222-224]. A five point difference in score is considered to be clinically meaningful [219]. Furthermore a change of 10 points in the physical function domain is considered reflective of significant clinical improvement in this measure in critically ill patients [225], and this has been shown to be the MCID for patients with chronic respiratory conditions [226, 227]. However MCID values for each domain of the SF-36, and each component score have yet to be determined for the post critical illness population.

2.5.2 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression scale (HADS) [228] comprises fourteen questions that detect symptoms of anxiety and depression (*Appendix III*). The questionnaire can be self-completed or researcher-administered. Total scores, and component anxiety and depression scores, can be obtained. Higher scores indicate a worse level of HRQL. In ICU survivors, the HADS has been shown to perform as well as other anxiety and depression scores for symptom detection [114].

2.6 Assessment of peripheral skeletal muscle strength

In this thesis, the target peripheral skeletal muscle group was quadriceps femoris, and the target muscle was rectus femoris. The rational for focussing on this muscle group was its functional importance in many activities such as standing, stepping and walking. For this reason, the London Respiratory Muscle Group and King's Health Partners Clinical Respiratory Physiology Group have developed extensive experience in the measurement of both quadriceps muscle strength, and rectus femoris cross-sectional area in both healthy subjects and a range of clinical conditions.

2.6.1 Quadriceps maximum voluntary contraction and twitch tension

Quadriceps strength was assessed using the technique of isometric maximum voluntary contraction (QMVC), and twitch tension (TwQ) following magnetic stimulation of the femoral nerve. Equipment set-up was similar to the previous description of a strength-testing bench system [74] (Figure 2-2). Subjects were positioned near supine on a purpose-built plinth that allowed the lower leg to be fixed at 90^{o} knee flexion. The ankle was placed in an inextensible strap approximately one inch above the lateral malleolus which was then connected to a strain gauge (Strainstall UK Ltd, Cowes, UK; range 0-100kg). Position of the strain gauge strap parallel to the quadriceps was checked, and care was taken to avoid any slack in the strap between the strain gauge and the ankle. Analogue force signals from the strain gauge were amplified using a Biomedical Amplifier Pclab-3808 (Beijing Microsignal Technology Development Company Limited, China),

converted to digital using a 16s Powerlab® unit (ADInstruments Pty Ltd, Castle Hill, Australia) with processing and analysis by Chart™ software (Version 7.1, ADInstruments Pty Ltd). A two-point calibration test (0kg and a known weight of 24.6kg) was performed prior to each use of the equipment.

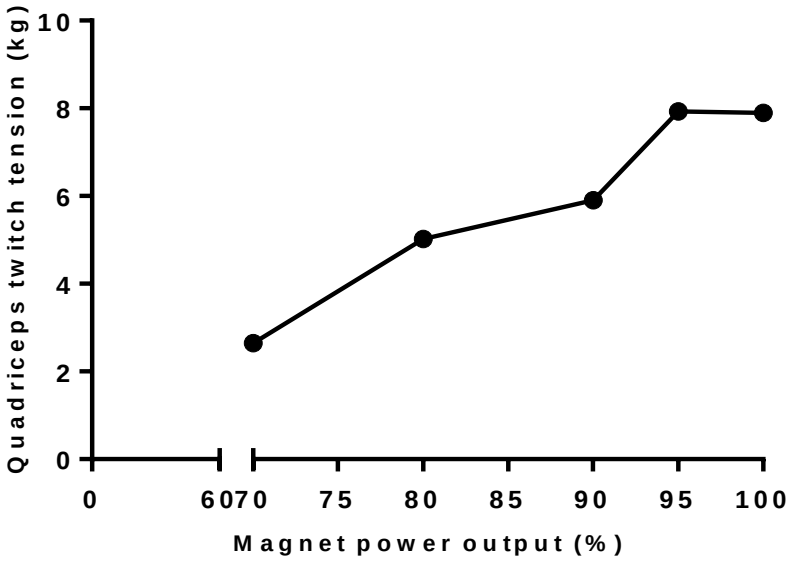
Participants performed isometric contractions with standardised verbal encouragement until a minimum of three technically acceptable traces within 5% were obtained. Values reported for QMVC were the highest mean tension recorded over a 1 second period. All measures were taken from the right leg.

Quadriceps twitch tension was measured adopting the method of Polkey *et al* [64]. Unpotentiated twitches were obtained following 20minutes of rest to minimise twitch potentiation. Twitch potentiation is a physiological phenomenon whereby the magnitude and duration of a preceding contraction can influence twitch response [78, 79]. With subjects positioned in the strength testing bench, femoral nerve stimulation was performed using a 70mm figure-of-eight coil (Magstim Co. Ltd, Whitland, UK) powered by a Magstim® 200 magnetic stimulator (Magstim Co. Ltd, Whitland, UK).

Figure 2-2 Quadriceps maximum voluntary contraction and twitch tension

Sequence of images demonstrating subject set-up for quadriceps maximum voluntary contraction and operator application of femoral nerve stimulation for twitch tension. From left to right: subject position in quadriceps bench, with operator position for application of femoral nerve stimulation; positioning of figure-of-eight coil; ankle positioned in inextensible strap attached to strain gauge.

The femoral arterial pulse was palpated to facilitate initial placement of the coil head high in the femoral triangle immediately lateral to this point over the femoral nerve. Further minor adjustments ensured optimum stimulation site, and supra-maximality of the response was determined. Supramaximal stimulation is required to ensure maximum force generation, and was achieved through stimulation at various power outputs (70%, 80%, 90%, 95%, 100%) of the magnetic stimulator in a random order such that further increases in stimulation intensity did not elicit further increases in twitch tension. A graph of twitch tension against power output was then generated with supramaximality judged a twitch tension with less than 5% difference compared with the lower output stimulation (Figure 2-3).



(Actual values: 70%=2.66kg. 80%=5.02kg. 90%=5.91kg. 95%=7.93kg. 100%=7.89)

Figure 2-3 Magnet power output against quadriceps twitch tension

Quadriceps twitch tension (TwQ) was recorded as the mean of 10 maximal responses at 100% of magnetic stimulator power output. Brief rest periods between twitches minimised twitch-on-twitch potentiation. The level of voluntary quadriceps activation was determined using the twitch interpolation measure [229, 230]. Superimposed twitches were applied during QMVC on direct observation of a plateau in force generation (Ts) and immediately after relaxation of the quadriceps (Tr) i.e. a potentiated twitch (Figure 2-4). The Ts:Tr ratio,

expressed as a percentage, calculates the proportion of voluntary muscle activation.

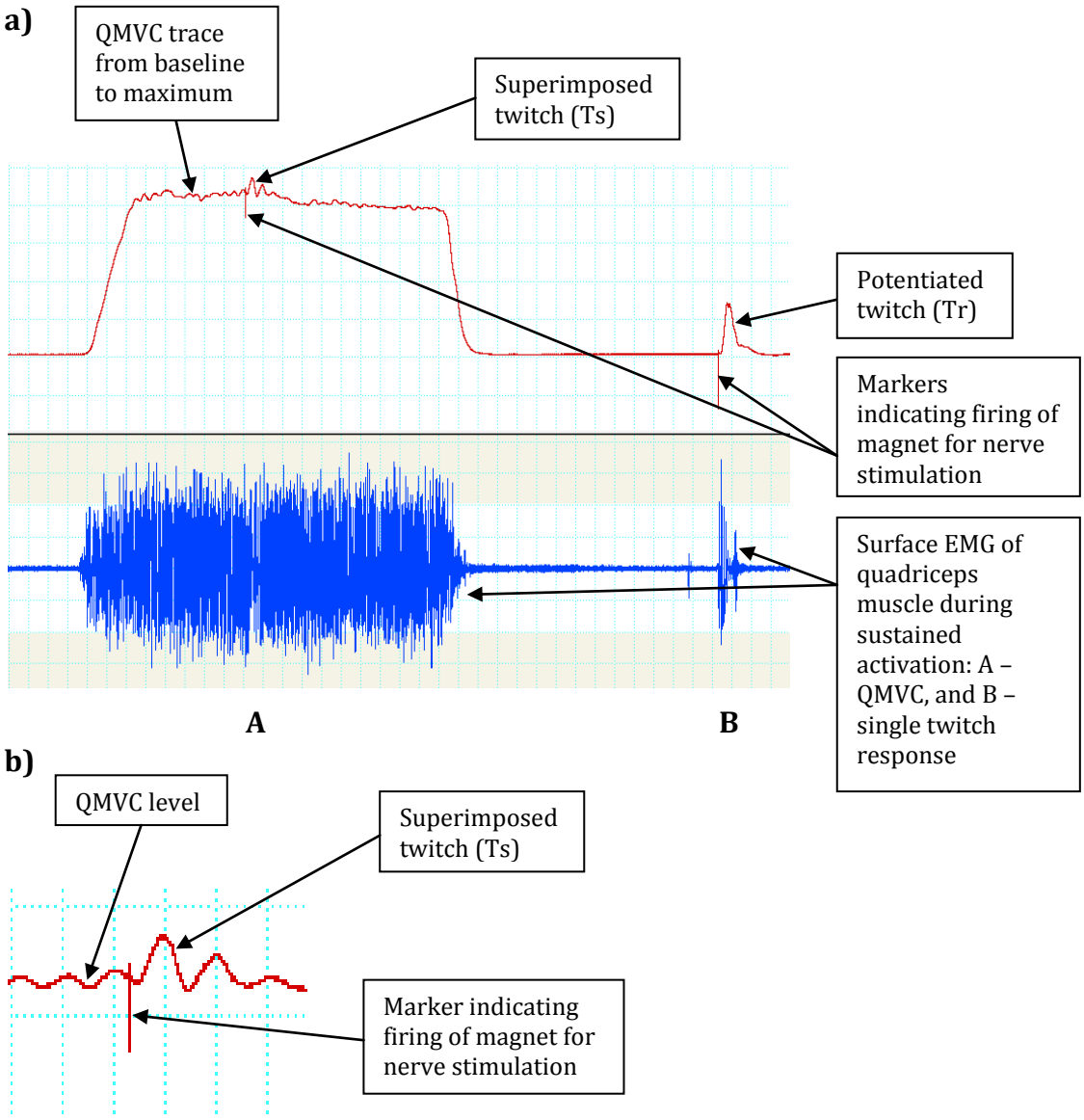
Voluntary activation (%) = (1–(Ts/Tr))*100

A truly maximal voluntary activation elicits a superimposed twitch with an amplitude of zero i.e. no further tension generation, with a linear increase in twitch amplitude observed as intensity of voluntary contraction decreases [231].

Magnetic stimulation has few reported side-effects but contraindications to its use include the presence of cardiac devices and/or metallic objects within the magnetic field [231].

2.6.1.1 Electromyography

Surface electromyography (EMG) of the rectus femoris muscle was also measured to confirm supra-maximal femoral nerve stimulation (Figure 2-4). The skin directly over the muscle belly was prepared using an abrasive gel (NuPrep, Weaver and Company, Aurora, USA) and then wiped clean with alcohol wipes. Once dry, three electrodes (ECG electrodes, ARBO*, Tyco Healthcare, Germany) were sited. Two electrodes were positioned over the muscle belly and a third earthed electrode over the patella. EMG signals were amplified using a Biomedical Amplifier Pclab-3808 (Beijing Microsignal Technology Development Company Limited, China) with a gain of 1000 and band-pass filtered between 10Hz and 3kHz, then converted to digital using a 16s Powerlab® unit (ADInstruments Pty Ltd, Castle Hill, Australia) with subsequent processing and analysis performed on a computer running Chart™ software (Version 7.1, ADInstruments Pty Ltd).



a) Traces of quadriceps maximum voluntary contraction (QMVC) and quadriceps surface electromyography (EMG) indicating superimposed and potentiated twitches

b) Detail of superimposed twitch evident above level of QMVC (magnified trace)

Figure 2-4 Traces obtained during quadriceps maximum voluntary contraction and magnetic stimulation of femoral nerve

2.6.1.2 Linearity of the QMVC strain gauge

Linearity of the strain gauge used in the assessment of QMVC was demonstrated using a pre-determined set of weights applied sequentially to the strain gauge. Values of absolute weight and corresponding strain gauge output were measured to determine a linear relationship. The strain gauge was found to be linear across a 0-50.9kg range (Figure 2-5).

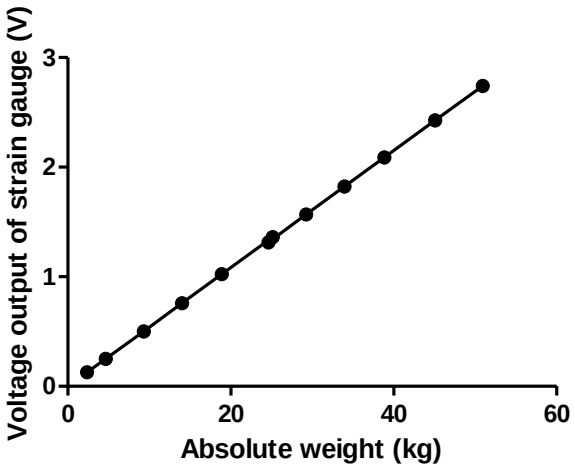


Figure 2-5 Linearity of the quadriceps strain gauge

2.6.1.3 Frequency response of the QMVC strain gauge

Frequency response (Fr) of the strain gauge was measured by the immediate release of a known weight from the strain gauge. The response time was the time taken for the force to reduce from 90% to 10%, and Fr determined using the equation below:

Fr = 1/(3*response time)

For the strain gauge used in this system, response time=0.03005ms resulting in Fr=11.09Hz, which is acceptable for measuring quadriceps twitch force in healthy humans and patients with disease.

2.6.1.4 Reproducibility of TwQ and Tr measurements

To ensure a standardised approach the reproducibility of TwQ and Tr measurements were determined through repeated assessments made by the same investigator (BC) on the same healthy subject on the same day. Three measurements were taken that were separated by a minimum of 30 minutes. Table 2-2 reports the mean co-efficients of variation of 7.7% and 6.2% for TwQ and Tr respectively.

Table 2-2 Reproducibility of quadriceps twitch tension and potentiated twitch measurements

Subject	Measurement (kg)	Occasion			Mean	SD	CV (%)
		1	2	3			
1	TwQ	19.3	14.9	15.1	16.4	2.0	12.2
	Tr	23.9	21.6	22.0	22.5	1.0	4.4
2	TwQ	6.1	6.6	5.5	6.1	0.4	7.3
	Tr	10.7	11.2	10.1	10.6	0.5	4.5
3	TwQ	7.4	6.5	6.5	6.8	0.4	5.9
	Tr	17.2	12.3	13.9	14.5	2.0	14.1
4	TwQ	7.7	6.5	6.5	6.9	0.6	8.3
	Tr	9.9	9.0	10.1	9.6	0.5	5.1
5	TwQ	10.6	9.9	9.4	10.0	0.5	5.0
	Tr	14.4	13.6	13.6	13.9	0.4	2.8
Mean	TwQ				9.2	0.8	7.7
	Tr				14.2	0.8	6.2

Abbreviations: TwQ = quadriceps twitch tension. Tr = potentiated quadriceps twitch force. SD = standard deviation. CV = coefficient of variation

2.6.2 Handgrip dynamometry

Maximal isometric hand-grip force was measured using a hand dynamometer (Baseline, Fabrication Enterprises Incorporated, Irvington, NY, USA) (Figure 2-6). There are five handle positions on the dynamometer, and the handle was adjusted to the position that ensured that the proximal interphalangeal joints rested on the top. Maximum grip strength has been found using position 2 [232]. Subjects were seated upright, with shoulders adducted and neutrally rotated, and elbows flexed to 90^{o} unsupported and without touching the trunk [233]. The dominant side was tested [36]. Standardised encouragement was provided to subjects to exert maximal force on the dynamometer. Five technically acceptable tests were performed and the maximum result in kilograms was reported as handgrip strength.

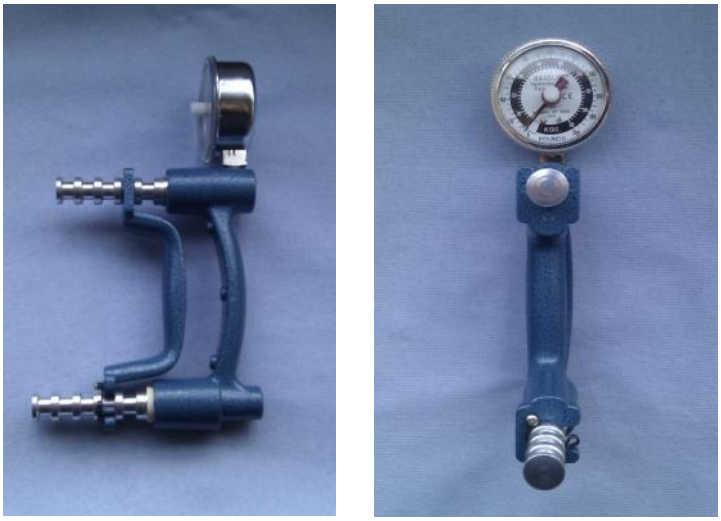


Figure 2-6 Baseline dynamometer

(L) side profile with different hand positions visible and set up for handgrip position 2. (R) front profile with reading gauge visible

Normal handgrip strength values for both left and right side, gender and across twelve age groups have been determined [44]. Handgrip dynamometry has been successfully performed in ICU patients where cut-off values of less than 11kg for males and less than 7kg for females, whilst well below age-matched and sex-matched control values, have been reported to indicate ICU-AW [36]. Indeed handgrip strength has been shown to be independently associated with hospital mortality [36].

2.6.2.1 Linearity of the dynamometer

Linearity of the dynamometer was demonstrated using a method outlined by Fess [234]. The dynamometer was fixed in a secure position allowing addition of progressively greater weights to be suspended from the device. Readings were taken for each weight added, and the process repeated for each handle position (Position 1-5). The dynamometer was found to be linear across the range 0-27.3kg for each of the handle positions (Figure 2-7).

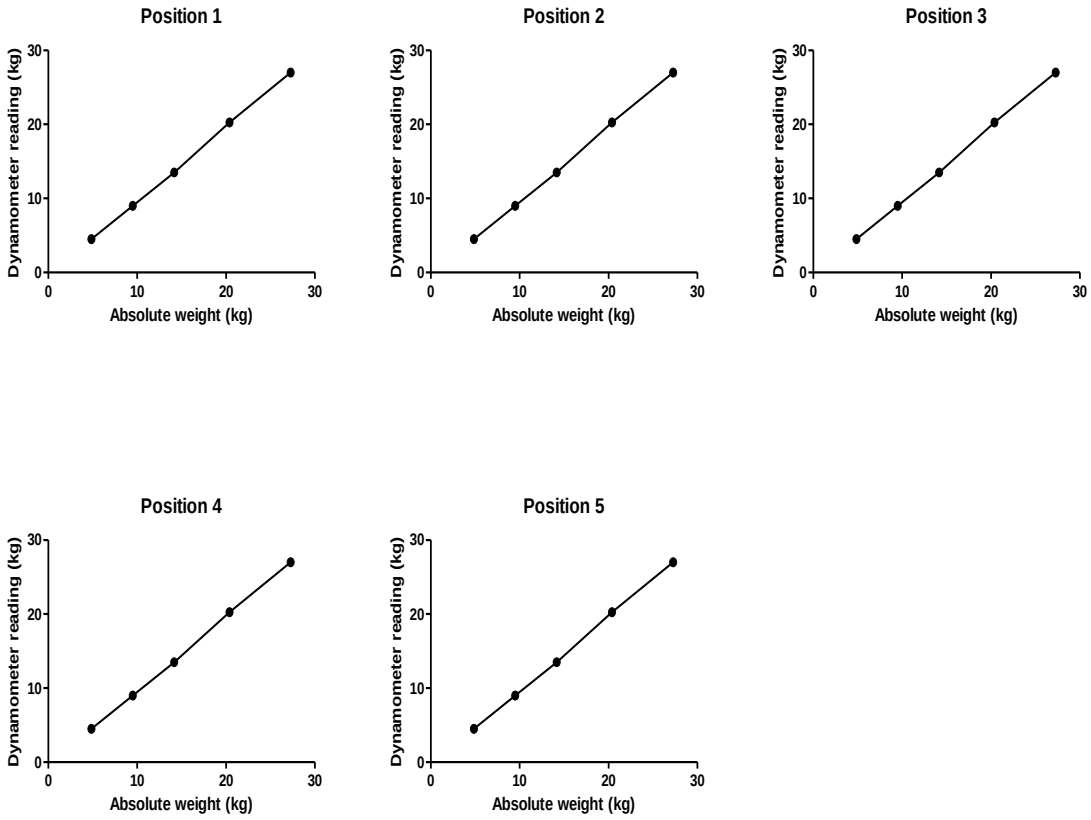


Figure 2-7 Linearity of the Baseline dynamometer

2.7 Assessment of peripheral skeletal muscle architecture

2.7.1 Quadriceps rectus femoris cross-sectional area

Cross-sectional area of the quadriceps rectus femoris muscle (RF_{CSA}) was determined using real-time B-mode ultrasonography using an 8MHz 5.6cm linear transducer (PLM805, Toshiba Medical Systems Ltd, Crawley, UK) and a 5MHz curvilinear transducer (C60x, Sonosite S Series Ultrasound, Hitchin, UK) using a method similar to that reported by Seymour *et al* [73] and de Bruin *et al* [95]. Distance from the anterior superior iliac spine (ASIS) to the superior patellar border was measured and two points marked on the thigh, at three-fifths of this distance and at two-thirds. The transducer was placed perpendicular to the long axis of the thigh on the superior aspect, on the two marked points and images recorded at both these points. Subjects were positioned semi-supine with the leg rested in passive extension. Liberal application of ultrasound gel (Aquasonic 100,

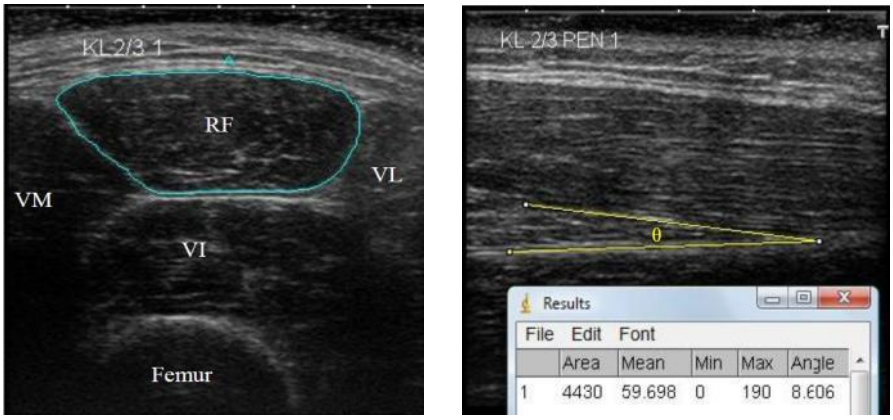
Parker Laboratories, Fairfield, NJ, USA) facilitated image quality, and the author used visual feedback to obtain the smallest cross-sectional area in each image. Visualisation of the femur acted as a marker for scanning depth. Subjects were instructed to gently contract and relax their quadriceps muscle to assist in discerning the muscle outline prior to image acquisition. Care was taken to avoid application of excess pressure during scanning which would compress the underlying muscle [84]. The inner echogenic line of the rectus femoris was outlined to indicate RF_{CSA}, which was calculated using either a planimetric technique online (Nemio™, Toshiba Medical Systems Ltd, Crawley, UK), or offline using relevant software (Image J, U.S. National Institutes of Health, Maryland USA, http://rsb.info.nih.gov/ij/) (Figure 2-8). To facilitate this process a reference distance caliper was marked and saved on the frozen image. RF_{CSA} was taken as the average of three measurements within a maximum of 10%.

2.7.2 Quadriceps rectus femoris pennation angle

Rectus femoris pennation angle (RF_{PA}) was also measured at both points i.e. three-fifths and two-thirds distance between ASIS and superior patellar border, by placing the transducer parallel to the long axis of the thigh in the direction of muscle fibres in the mid-point of the marker line for each distance point. Image acquisition occurred when individual muscle fibres of rectus femoris inserting into the muscle aponeurosis between rectus femoris and vastus intermedius were visible [93, 97, 99, 102] (Figure 2-8). Offline software was used to calculate pennation angle (Image J, U.S. National Institutes of Health, Maryland USA, http://rsb.info.nih.gov/ij/) which was considered to be the angle between muscle fibre and aponeurosis [93].

2.7.3 Reproducibility of ultrasound measurements

Reproducibility of ultrasound measurements (RF_{CSA}) was determined through repeated assessments taken on the same subject on the same day. These data are presented in detail in *Chapter 4*.



A **B**

Figure 2-8 Ultrasonographic images of rectus femoris muscle structure

(A) RF_{CSA} as indicated by blue outline of RF muscle, other structures also identified. (B) RF_{PA} where θ is the angle between insertion of muscle fibre into aponeurosis.

Abbreviations: RF = rectus femoris. VM = vastus medialis. VI = vastus intermedius. VL = vastus lateralis. Θ = pennation angle.

2.7.4 Calibration of online ultrasound measuring

To confirm measurement accuracy of the online ultrasound measuring system (planimetric technique, Nemio™, Toshiba Medical Systems Ltd, Crawley, UK), an item of known dimensions was placed in a scan-able medium and measured. Figure 2-9 demonstrates the images gained from measurement of a 10ml Luer syringe with known diameter of 17.2mm (Terumo UK Ltd, Egham, UK), and circumference of 54mm (using circumference=πd where d=17.2mm). One image only is shown; in practice three were taken (53.4mm, 54.1mm, 53.9mm) with an average circumference of 53.8mm. The average measured circumference shows a 0.38% variation from the actual circumference.

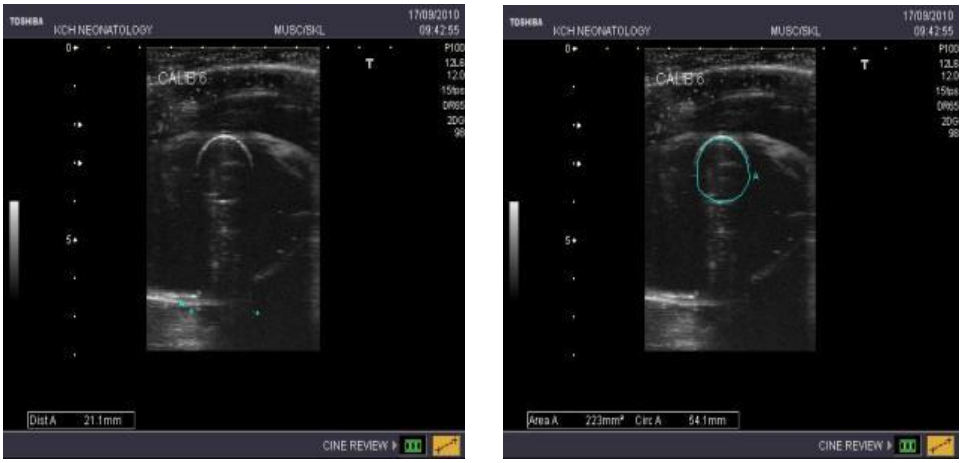


Figure 2-9 Ultrasound images of reference measurement item for calibration of ultrasound machine

(*L) unmeasured. (R) measured with circumference outlined in blue*

2.7.5 Agreement between online and offline image measurement

To determine the level of agreement between online (planimetric technique, Nemio™, Toshiba Medical Systems Ltd, Crawley, UK) and offline (Image J, U.S. National Institutes of Health, Maryland USA, http://rsb.info.nih.gov/ij/) ultrasound image measurement processes, results of 117 images of RF_{CSA} measured using both systems were analysed. Bland-Altman analysis, (Figure 2-10), demonstrated mean differences between the two modes of measurement (95% limits of agreement -7.5 to 5.6mm^2.mean (SD) bias -0.9 (3.3)mm^2). An ICC of 1.0 (95%CI, 1.0-1.0) was observed.

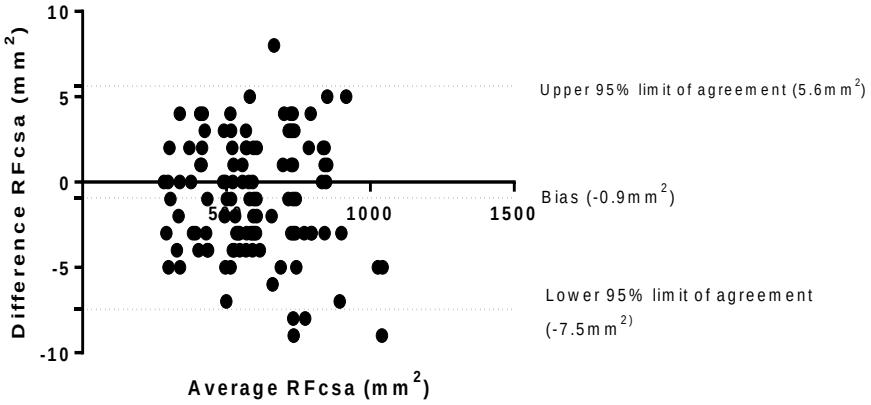


Figure 2-10 Bland Altman analysis of agreement between online and offline ultrasound image measurement

2.8 Anthropometrics

Fat-free mass was determined using bio-electrical impedance analysis (Bodystat® 1500, Bodystat®, Isle of Man, UK). Subjects rested in a semi-supine position for at least 5minutes prior to placement of four electrodes, one below the right second metacarpal head, a second adjacent to the right ulnar head, a third below the right first metatarsal head and a fourth between the level of the right medial and lateral malleoli. Participants with electrical cardiac devices in situ were excluded from these measurements to avoid potential interference with electrical signals from these devices that could result in cardiac symptoms.

The Bodystat® 1500 automatically internally self-calibrates with each measurement performed. However periodic independent checks (physical re-calibration can only be performed by the manufacturer) were also performed using the specific Bodystat® calibrator supplied with the device in keeping with the recommended procedure (Bodystat®). On all occasions results were the same as those indicated by the manufacturer.

2.9 Physical function

2.9.1 Barthel Index

The Barthel Index [235] is a scale rating ability across a range of personal and functional activities of daily living. Higher scores indicate more independent performance and hence a higher level of functional ability. The index is used commonly within hospital settings and across a range of patient groups.

2.9.2 Timed Up and Go

The Timed Up and Go test (TUAG) [236] measures the speed with which an individual can stand up from a chair, mobilise three metres and return to their seated position. Assistance required to perform this manoeuvre e.g. mobility aid, or using arms of the chair to assist with standing is also noted.

2.9.3 Sit to Stand 5

The Sit to Stand 5 times test (STS-5) [237] measures the speed at which an individual can stand up and sit down from the same chair five times, and the assistance required to do so e.g. ranging from use of arms of the chair, to standing completely independently with hands across chest.

2.10 Statistical analysis

Statistical analysis of the data were performed using GraphPad Prism version 6.00 for Windows (GraphPad Software, La Jolla California USA, www.graphpad.com), and IBM SPSS Statistics Data Editor version 19 for Windows (IBM, US). Power calculations were performed using G*Power version 3.1.3 (Universitat Kiel, Germany) Data were tested for normality using D'Agostino and Pearson, and Shapiro-Wilk normality tests, and appropriate parametric or non-parametric analyses applied. A p value of less than 0.05 was considered statistically significant. A range of statistical analyses are used in this thesis and are discussed in each relevant chapter.

Chapter 3 Inter-observer agreement and clinical predictive value of the Medical Research Council sum-score

3.1 Introduction

Intensive care unit-acquired weakness (ICU-AW) [238] is the clinical term given to peripheral skeletal muscle wasting and dysfunction that develops as a consequence of critical illness, and which is a major factor contributing to both short- and long-term outcome in survivors [103-105, 194]. Furthermore ICU-AW, and the resulting physical and functional impairment, is a significant component of post intensive care syndrome [125]. The diagnosis of ICU-AW is based on a simple clinical 'bedside' examination involving volitional strength assessment in the form of manual muscle testing, most notably the Medical Research Council sum-score [35]. An MRC-SS of less than 48 out of a maximum of 60 is considered diagnostic of ICU-AW [5]. Although this volitional method of peripheral muscle strength assessment is appealing in the clinical setting as it is both simple and rapid to perform, and requires limited expert operator and technical input, there are a number of caveats to its use in the critically ill population. Inability to perform the test or obtaining a low value may occur as a result of non-muscular factors such as impaired cognition, reduced conscious level and poor motivation. Furthermore, the ordinal nature of grading muscle strength results in potential variability in both application of testing and interpretation of results between clinicians [52]. These limitations have led to contrasting data for diagnosing ICU-AW within the ICU as well as variability in the inter-observer agreement of the MRC-SS in ICU patients with differing levels of weakness [38, 59, 60].

Nonetheless ICU-AW based on MRC-SS assessment has a reported prevalence of up to 65%, with observational studies showing associations with prolonged weaning, delayed rehabilitation, increased hospital length of stay and increased mortality [11, 29, 30, 36, 37, 40-42]. However such observational cohort studies do not necessarily demonstrate a causal relationship, nor has the association between global peripheral skeletal muscle strength represented by the MRC-SS and physical function been examined. Furthermore, as a diagnostic test there are currently no reported data examining the clinical predictive value and test characteristics of the MRC-SS for key outcomes such as length of stay and mortality. The principles of establishing the diagnostic performance of the MRC-SS will now be discussed.

3.1.1 Diagnostic test performance characteristics

The clinical merit and utility of any diagnostic test for a disease or condition involving a binary classification, can be evaluated by determining its accuracy expressed in a number of different test characteristics, based on the ability of the test to correctly classify individuals according to their disease status or condition. Typically these properties can be expressed schematically in a 2x2 contingency table (Figure 3-1).

		Disease/condition		
		Positive	**Negative**	
Test outcome	**Positive**	**TP**	**FP (type I error)**	**PPV TP/(TP+FP)**
	Negative	**FN (type II error)**	**TN**	**NPV TN/(FN+TN)**
		Sensitivity TP/(TP+FN)	**Specificity TN/(FP+TN)**	

Figure 3-1 2x2 contingency table for determining diagnostic test characteristics for a condition or disease

Abbreviations: TP = true positive. FP = false positive. FN = false negative. TN = true negative. PPV = positive predictive value. NPV = negative predictive value.

In Figure 3-1, the 'true positives' (TP) are those individuals correctly diagnosed with the disease or condition and correctly accepted by the test; 'false positives' (FP) are those healthy individuals incorrectly identified with the disease or condition and incorrectly accepted by the test (type I error); 'true negatives' (TN) are those individuals correctly identified without the disease or condition and correctly rejected by the test, and 'false negatives' (FN) are those individuals with the disease or condition incorrectly identified as without the disease or condition and incorrectly rejected by the test (type II error).

Figure 3-2 outlines this concept for the current study, using the example of the MRC-SS for diagnosing ICU-AW, and clinical outcomes of ICU and hospital, mortality and length of stay (LOS).

		ICU Mortality Hospital Mortality ICU LOS* Hospital LOS#		
		Dead or >14days* or >28days#	**Alive or ≤14days* or ≤28days#**	
MRC-SS	**UTP or <48/60**	**TP**	**FP (type I error)**	**PPV TP/(TP+FP)**
	ATP or ≥48/60	**FN (type II error)**	**TN**	**NPV TN/(FN+TN)**
		Sensitivity TP/(TP+FN)	**Specificity TN/(FP+TN)**	

Figure 3-2 2x2 contingency table for determining diagnostic test characteristics for Medical Research Council sum-score for clinical outcomes of mortality and length of stay

Abbreviations: MRC-SS = Medical Research Council Sum-score. ICU = intensive care unit. LOS = length of stay. UTP = unable to perform. ATP = ability to perform. TP = true positive. FP = false positive. FN = false negative. TN = true negative. PPV = positive predictive value. NPV = negative predictive value.

Here, the binary classifications are firstly ability to perform the test and inability to perform the test, and secondly diagnosis of ICU-AW using the previously reported 'cut-off' of less than 48 out of 60. Each of these classifications is then considered against outcomes of different 'conditions', namely, ICU mortality (dead/alive), hospital mortality (dead/alive), ICU LOS (>14days/≤14days) and hospital LOS (>28days/≤28days) (Figure 3-2). True positives refer to those patients unable to perform the test or diagnosed with ICU-AW (MRC-SS <48/60) with associated ICU or hospital mortality, or LOS of greater than 14days and 28days for ICU and hospital LOS respectively. False positives are those patients unable to perform the test or diagnosed with ICU-AW who are alive at ICU and hospital discharge or with LOS of less than 14days and 28days for ICU and hospital LOS respectively. True negatives are those patients able to perform the test or without ICU-AW (MRC-SS ≥48/60), and who are alive at ICU and hospital discharge or with a LOS of less than 14days and 28days for ICU and hospital LOS respectively. Finally, false negatives are those patients who are able to perform the test or without ICU-AW, with associated ICU or hospital mortality or protracted LOS.

3.1.1.1 Sensitivity and specificity

Sensitivity of a diagnostic test relates to its ability to identify positive results, measuring the proportion of true positives which are correctly identified as such. It can be considered as the probability of a positive test, if a patient has a disease or condition. Diagnostic tests with high sensitivity can be considered reliable indicators for ruling out disease when results are negative, since true positives are nearly always identified (low type II error rate). Conversely, specificity relates to a test's ability to identify negative results, and measures the proportion of correctly identified true negatives. Specificity is the probability of a negative test result if the patient is well. Highly specific tests rarely miss negative outcomes, and hence can be considered reliable for ruling in a disease when results are positive (low type I error rate). However false positives are not accounted for when calculating sensitivity nor false negatives when determining specificity. In clinical practice, the ideal test demonstrates very high sensitivity and specificity allowing identification of the majority of true cases, and exclusion of the majority of non-cases. However in reality there is a balance between achieving optimal levels of either characteristic depending on the diagnostic threshold level for each test. Levels ranging between 0.7 and 0.9 represent clinically useful tests [239] although this will also be dependent on the circumstances of test use.

3.1.1.2 Receiver operating characteristic curve

Receiver operating characteristic (ROC) curves are graphical representations of the balance between relative sensitivities and specificities of diagnostic tests at varying discriminatory thresholds. Sensitivity, or true positive rate, is plotted on the y-axis, and false positive rate (1-specificity) on the x-axis. ROC analysis can assist in identifying alternative diagnostic thresholds with more clinically appropriate sensitivity and/or specificity than demonstrated on existing values.

3.1.1.3 Positive and negative predictive value

Positive (PPV) and negative (NPV) predictive value further reflect the clinical application of tests and are influenced by the known true prevalence of a disease

or condition in a population. The PPV is the proportion of positive results that are true positives, and the NPV, the proportion of negative results that are true negatives (Figure 3-1).

3.1.2 Aims of study

The aims of this study were fourfold, focussing on the use of the MRC-SS for diagnosis of ICU-AW:

1. To investigate the differences in inter-observer agreement of ICU-AW in critically ill patients within the ICU and in simulated presentations of weakness
2. To determine a) the clinical predictive value of ability to perform the MRC-SS at awakening and b) the clinical predictive value of an MRC-SS less than 48 out of 60 at awakening in critically ill patients
3. To investigate the relationship between ICU-AW and handgrip strength
4. To investigate the relationship between ICU-AW and physical function

3.2 Method

3.2.1 Study design

This was a two-part, observational study. *Study 1* determined inter-observer agreement of MRC-SS in ICU patients and simulated weakness presentations. Ethical approval was granted from the local ethical review board and written informed consent was gained from all participants. *Study 2* investigated the clinical predictive value of (a) ability to perform MRC-SS at awakening and (b) MRC-SS indicative of ICU-AW. In addition, in *Study 2*, the relationship between awakening MRC-SS, and subsequent diagnosis of ICU-AW and handgrip strength and physical function at ICU discharge was also investigated. The local hospital ICU audit committee approved *Study 2* as a clinical service evaluation and hence informed consent was not deemed necessary.

3.2.2 Participants

Patients ≥18years and invasively mechanically ventilated for ≥48hours were eligible for inclusion. Exclusion criteria included neurological weakness, requirement for acute non-invasive ventilation, pregnancy, malignancy, palliation-only orders and those admitted for routine overnight post-operative surgical recovery. Separate patient cohorts were recruited for *Study 1* and *2.* A healthy volunteer was recruited for *Study 1*.

3.2.3 Screening for awakening and assessment of peripheral muscle strength

Conscious level of patients in both *Study 1* and *Study 2*, was determined using the Richmond Agitation Sedation Scale (RASS) [49]. The RASS is an ordinal scale ranging from -5 (unrousable) to +4 (combative behaviour), including 0 (alert and calm) and a nominal 'A' indicating the subject is asleep. A score of -1 (drowsy) to +1 (restless) was considered indicative of wakefulness.

Awake patients were then required to demonstrate positive response to four simple one-stage commands including 'Open and close eyes', 'Stick out your tongue' and 'Squeeze my fingers'. Successful completion of these commands was followed by muscle strength assessment using the MRC-SS. This is a 6 point grading scale ranging from 0 (no visible contraction) to 5 (normal power) applied to six upper and lower limb muscle groups bilaterally [35] (Chapter 2.3) ICU-AW was defined as an MRC-SS less than 48 out of 60 [30, 36, 40, 41, 240]. The protocol for screening for awakening and assessment of peripheral muscle strength is in keeping with previous reported studies investigating the MRC-SS and ICU-AW [11, 36, 37].

Two specialist physiotherapists with extensive clinical expertise in rehabilitation of critically ill patients including muscle strength assessment, conducted MRC-SS assessments. A standardised protocol for performing the MRC-SS was followed at all times during testing (*Appendix 1*). Given the volitional nature of manual muscle testing, strong verbal encouragement was provided during all strength

assessments. Examiners tested each patient in the same position (supine or seated).

3.2.4 Study 1 - Inter-observer agreement of MRC-SS

A pragmatic sample size of 20 patients was chosen for this study. ICU patients underwent MRC-SS testing, performed by both examiners separated by a minimum of 30 minutes. Initial testing order between examiners of the first patient was randomly assigned by concealed envelope and subsequent patient testing order followed an alternating pattern. MRC-SS value scored by the first testing clinician on each occasion was defined as the reference score.

For assessment of simulated weakness, one healthy volunteer was trained comprehensively in the MRC-SS, including muscle groups assessed and the different potential levels of weakness (ranging 0-5). After a practice period the healthy volunteer was then instructed to simulate the 20 reference scores in a random order, which were re-scored by both clinicians. Clinician order of testing was again random for the first presentation, following an alternating pattern thereafter. Both clinicians adopted the standard operating protocol for performing MRC-SS, and the healthy volunteer simulated the weakness presentations in the same position (seated or supine) as the original patient was tested. At each stage both clinicians were blinded to each other's and the reference score.

3.2.5 Study 2 - Clinical predictive value of the MRC-SS and relationship with physical function and handgrip strength

Daily screening of ICU patients for eligibility and suitability for MRC-SS testing occurred over a three month period. MRC-SS were obtained at awakening, defined as the first occasion on which an MRC-SS could be measured, and at seven days post awakening, and compared against outcomes of ICU and hospital mortality, and length of stay (LOS). Awakening scores were used to determine association with prospective outcomes. Prolonged length of stay was defined *a priori* as greater than 14days and greater than 28days for ICU and hospital LOS respectively.

Patients alive at ICU discharge also completed assessment of physical function and handgrip strength performed within 72hours of ICU discharge. This time-point was pragmatic in selection, ensuring availability of either examiner to perform assessments, and allowing sufficient time to ensure clinical stability of patients following ward transfer. Physical function measures included the Barthel scale [235], a measure of functional activity performance commonly used in the in-patient setting covering aspects of personal care, mobility and transfers and the Elderly Mobility Scale (EMS) [241], a validated tool for assessing mobility in frail, elderly subjects. It includes assessment of functional transfers, balance and gait performance that may be applicable to the early stages of the rehabilitation process for post ICU patients. Handgrip strength was measured using dynamometry.

3.2.6 Statistical analysis

3.2.6.1 Study 1

Inter-observer agreement between clinicians for the MRC-SS in ICU patients and simulated presentations was determined using intra-class correlation coefficients (ICC) calculated using a two-way random effects for absolute agreement [242], and percent agreement for total MRC-SS (total number of exact MRC-SS measurements/total number). Level of agreement for the binary outcome of ICU-AW (MRC-SS <48;≥48) was determined using Cohen's Kappa statistic with a grading system from 'poor' to 'complete' agreement [243].

Inter-observer agreement was further evaluated by analysing individual muscle group scores from ICU patients, again using ICC and Kappa techniques. This process was repeated for individual muscle group scores from simulated presentations, and furthermore for analysing each clinician's simulated MRC-SS results against the reference score for both total scores and individual muscle group scores. Where applicable agreement for the binary outcomes of ICU-AW (MRC-SS <48 and ≥48) and individual muscle group weakness (MRC score <4 and ≥4) were employed. Median individual muscle group scores for each clinician

were compared using Wilcoxon signed rank testing. A *p* value <0.05 was considered statistically significant.

3.2.6.2 Study 2

Initial analysis involved Fisher's exact test to determine association between MRC-SS outcomes (ability to perform the test, and scoring <48/60) and clinical outcomes (ICU and hospital mortality, and ICU and hospital LOS). *A priori* an extended ICU length of stay was defined as greater than 14days, and greater than 28days for hospital LOS. Subsequent analysis of test characteristics (sensitivity, specificity, positive (PPV) and negative (NPV) predictive value) was then performed using an *a priori* cut-off of 75% to be clinically acceptable. Additional receiver-operator characteristic (ROC) analysis was performed on awakening MRC-SS measurements for each clinical outcome to assess sensitivity and specificity at levels of MRC-SS from 0 to 60.

Continuous data for awakening MRC-SS, physical function and handgrip strength were analysed using Spearman's correlation. Physical function and handgrip strength were then compared according to ICU-AW diagnosis (MRC-SS <48/60; MRC-SS ≥48/60) with Mann-Whitney analysis.

A *p* value <0.05 was considered statistically significant.

3.3 Results

3.3.1 Study 1 – Inter-observer agreement of the MRC-SS

3.3.1.1 Inter-observer agreement of the MRC-SS for ICU patients

Twenty patients participated in this study. Demographic and clinical data for the cohort are shown in Table 3-1. ICU LOS prior to MRC-SS testing was 24.0 (6.8-43.3)days, and 45% of patients were receiving invasive mechanical ventilation at the time of testing. All muscle groups were tested on all occasions. MRC-SS for each testing clinician was 48 (39-51) and 48 (38-51) (Figure 3-3). Table 3-2

reports the MRC-SS obtained during testing from both clinicians for each patient. Median time between each patient's testing by clinicians was 30 (29-33) minutes. Maximum difference in MRC-SS measurements for any one patient was 7 and agreement between clinicians' scores was 15.0%. The ICC was 0.94 (95%CI 0.85-0.98) and Kappa statistic for agreement on the diagnosis of ICU-AW was 0.60 (95% CI 0.25-0.95). There were seven patients for whom both clinicians agreed diagnosis of ICU-AW, and four where one clinician scored MRC-SS<48 and the other ≥48/60.

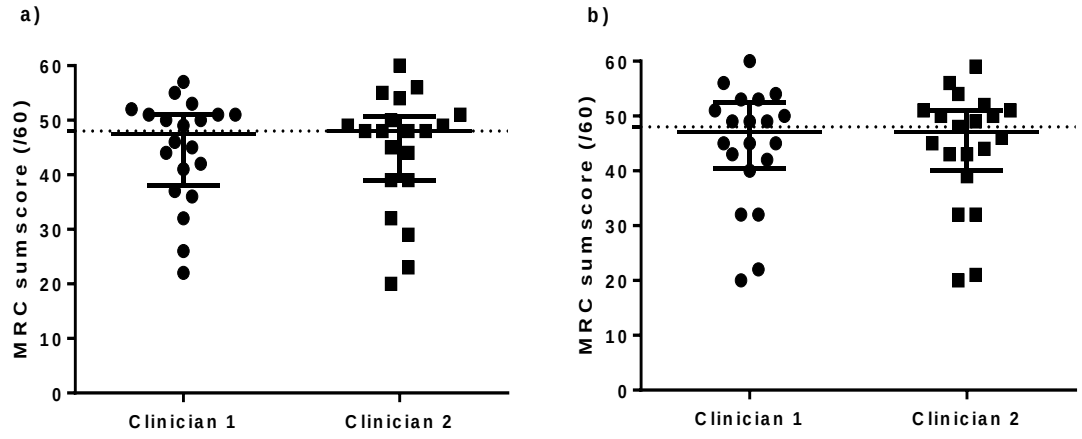


Figure 3-3 Medical Research Council Sum-Scores for clinician testing of critically ill patients and simulated presentations

a) MRC-SS values for critically ill patients for each clinician

b) MRC-SS values for simulated presentations for each clinician

Error bars indicate median and interquartile range. Dotted line indicates cut-off value of 48/60 below which indicates diagnosis of ICU-AW.

Abbreviations: MRC-SS = Medical Research Council sum-score. ICU = intensive care unit. ICU-AW = intensive care unit acquired weakness

Table 3-1 Demographic and clinical data for *Study 1* and *Study 2* cohorts

Characteristic	Range	
	Study 1: MRC-SS Inter-Observer Agreement n = 20	**Study 2: MRC-SS Clinical Predictive Value n = 94**
Age (years)	67.5 (51.8-75.0)	66.0 (54.8-76.3)
Gender (M:F)	12:8	64:30
APACHE II	19.5 (15.5-24.0)	17.0 (15.0-22.0)
Admission Type		
Medical (%)	70.0	78.7
Surgical (%)	30.0	21.3
Co-morbidity		
Chronic respiratory disease (%)	50.0	27.7
Chronic cardiac disease (%)	65.0	55.3
Chronic Renal disease (%)	5.0	4.0
Chronic Liver disease (%)	0.0	10.6
Total MV (days)	25.5 (21.0-44.0)	7.0 (4.0-16.0)
Total MV prior to MRC-SS testing (days)	21.0 (6.8-42.0)	n/a
ICU LOS total (days)	33.5 (25.5-58.0)	11.0 (6.0-25.3)
ICU LOS prior to MRC-SS testing (days)	24.0 (6.8-43.3)	n/a
Hospital LOS total (days)	52.5 (31.5-85.3)	27.0 (11.8-50.0)
Hospital LOS prior to MRC-SS testing (days)	23.5 (7.5-43.8)	n/a

Data are expressed as median (interquartile range (IQR)). For co-morbidities, values reflect % of cohort with specific organ disease with overlap across categories. Hence sum greater than 100%.

Abbreviations: ICU = intensive care unit. LOS = length of stay. MV = mechanical ventilation. APACHE = Acute Physiological and Chronic Health Evaluation. MRC-SS = Medical Research Council sum-score. n/a = not applicable

Table 3-2 Inter-observer agreement for MRC-SS critically ill patients; individual clinician scores

Patient	Clinician 1 MRC-SS (/60)	Clinician 2 MRC-SS (/60)
1	46	48
2	36	32
3	51	48
4	26	20
5	52	49
6	51	45
7	50	48
8	45	49
9	57	60
10	37	39
11	55	54
12	22	23
13	49	55
14	44	44
15	50	50
16	41	48
17	42	39
18	53	56
19	32	29
20	51	51

Abbreviations: MRC-SS = Medical Research Council sum-score

Inter-observer agreement of the MRC-SS in ICU patients was also determined for individual muscle groups tested (Table 3-3). Maximum percent agreement between clinicians was 75% for right knee extension and left ankle dorsiflexion. The strongest ICC for MRC scores of individual muscle groups was for left ankle dorsiflexion (0.86, 95%CI 0.68-0.94). Agreement for identification of weakness (MRC score <4:≥4) reported using Kappa statistic, ranged from 0.43-0.88. There was no evident trend towards a proximal-to-distal pattern of weakness distribution across upper or lower limb muscle groups, nor right and left symmetry.

Table 3-3 Inter-observer agreement for individual muscle group scores for critically ill patients

Muscle group	Kappa (95% CI)	ICC (95% CI)	% agreement
Shoulder Abd L	0.8 (0.54 – 1.06)	0.85 (0.67 – 0.94)	70
Shoulder Abd R	0.68 (0.35 – 1.01)	0.74 (0.46 – 0.89)	60
Elbow flexion L	0.69 (0.29 – 1.1)	0.69 (0.36 – 0.86)	65
Elbow flexion R	0.88 (0.64 – 1.11)	0.73 (0.43 – 0.88)	65
Wrist extension L	0.74 (0.39 – 1.08)	0.74 (0.46 – 0.89)	60
Wrist extension R	0.47 (0.06 – 0.87)	0.64 (0.27 – 0.84)	45
Hip flexion L	0.56 (0.18 – 0.95)	0.6 (0.22 – 0.82)	55
Hip flexion R	0.43 (0.001 -0.87)	0.76 (0.48 – 0.9)	60
Knee extension L	0.47 (0.06 – 0.87)	0.63 (0.28 – 0.84)	35
Knee extension R	0.57 (0.18 – 0.95)	0.69 (0.37 – 0.86)	75
Ankle DF L	0.83 (0.5 – 1.16)	0.86 (0.68 – 0.94)	75
Ankle DF R	0.86 (0.58 – 1.13)	0.77 (0.52 – 0.9)	45

Kappa statistic using binary outcome of clinical weakness (Medical Research Council score <4; ≥4). n=20

Abbreviations: Abd = abduction. DF = dorsiflexion. L = left. R = right. CI = confidence interval. ICC = intra-class correlation coefficient

Minimum, maximum and median scores for each clinician's individual muscle group score for ICU patients are shown in Table 3-4. No significant difference between each clinicians' median score for any muscle group was evident with the exception of right wrist extension (p=0.03). Although this muscle group demonstrated one of the widest 95% confidence intervals for Kappa agreement of weakness diagnosis, it was not the group with least percent agreement between clinicians (left knee extension).

Table 3-4 Individual muscle group scores for critically ill patients

Muscle group	Clinician 1			Clinician 2			p value
	Min	Max	Median (IQR)	Min	Max	Median (IQR)	
Shoulder Abd L	1	5	4 (2-4)	2	5	3.5 (3-4)	0.48
Shoulder Abd R	1	5	4 (2-4)	2	5	4 (3-4)	0.15
Elbow flexion L	2	5	4 (4-4)	2	4	4 (3.25-4)	0.07
Elbow flexion R	2	5	4 (3.25-4)	2	5	4 (3-5)	0.59
Wrist extension L	2	5	4 (4-4)	1	5	4 (3-4)	0.15
Wrist extension R	2	5	4 (2.25-4)	2	5	4 (4-5)	0.03
Hip flexion L	2	5	4 (2.25-5)	2	5	4 (3-4)	1.0
Hip flexion R	2	5	4 (2-5)	2	5	4 (3-4)	0.82
Knee extension L	1	5	4 (2-5)	2	5	4 (3-4.75)	0.42
Knee extension R	2	5	4 (2-5)	2	5	4 (2-5)	0.59
Ankle DF L	1	5	4 (4-5)	0	5	4 (4-5)	1.0
Ankle DF R	1	5	4 (4-5)	2	5	4 (2.5-4.75)	0.18

p values derived from Wilcoxon signed rank test for equality of median score. n=20.

Abbreviations: Abd = abduction. DF = dorsiflexion. L = left. R = right. Min = minimum score. Max =maximum score. IQR = interquartile range.

3.3.1.2 Inter-observer agreement for simulated MRC-SS presentations

These data were analysed in a similar manner. Median (IQR) MRC-SS measurements for the two clinicians were 47 (40-51) and 47 (41-53) (Figure 3-3). Table 3-5 reports MRC-SS obtained from both clinicians against the simulated reference score. Ten reference MRC-SS were <48/60 including four less than 36/60. On all occasions where the reference score was <48/60, both clinicians demonstrated agreement with this and confirmed the simulated ICU-AW presentation. Maximum difference between clinicians' scores was 2 with 45.0% agreement. ICC for simulated MRC-SS values was 1.0 (95%CI 0.99-1.0). Complete agreement for ICU-AW diagnosis was evident (Kappa 1.0 (95%CI 1.0-1.0)).

Table 3-5 Inter-observer agreement for MRC-SS in simulated weakness presentations; individual clinician scores

Patient	Reference score	Clinician 1 MRC-SS (/60)	Clinician 2 MRC-SS (/60)
1	20	20	20
2	44	43	44
3	22	22	21
4	60	60	59
5	56	56	56
6	52	53	51
7	32	32	32
8	50	49	50
9	32	32	32
10	50	50	50
11	42	42	43
12	54	54	54
13	39	40	39
14	45	45	43
15	45	45	45
16	48	49	48
17	46	45	46
18	49	49	49
19	51	53	52
20	51	51	51

Abbreviations: MRC-SS = Medical Research Council sum-score

Inter-observer agreement between the two clinicians for individual muscle groups assessed in simulated MRC-SS presentations is shown in Table 3-6. A minimum of 85% agreement between clinicians was demonstrated and ICC ranged from 0.93 to 1.0. For the majority of muscle groups, perfect agreement was demonstrated for the diagnosis of clinical weakness (MRC score <4; ≥4) as indicated by Kappa statistic of 1.0. The weakest level of agreement was for right hip flexion (Kappa 0.74). Albeit overall there were very high levels of agreement, there was no evident trend towards a proximal-to-distal pattern of weakness distribution across upper or lower limb muscle groups, nor right and left symmetry.

Table 3-6 Inter-observer agreement for individual muscle group sores for simulated weakness presentations

Muscle group	Kappa (95% CI)	ICC (95% CI)	% agreement
Shoulder Abd L	1.0 (1.0 – 1.0)	1.0 (1.0-1.0)	100
Shoulder Abd R	1.0 (1.0 – 1.0)	0.98 (0.95 – 0.99)	95
Elbow flexion L	0.86 (0.58 – 1.13)	0.96 (0.91 – 0.99)	95
Elbow flexion R	1.0 (1.0 – 1.0)	0.98 (0.94 – 0.99)	95
Wrist extension L	0.88 (0.64 – 1.11)	0.95 (0.88 – 0.98)	90
Wrist extension R	1.0 (1.0 – 1.0)	0.98 (0.95 – 0.99)	95
Hip flexion L	1.0 (1.0 – 1.0)	1.0 (1.0-1.0)	100
Hip flexion R	0.74 (0.39 – 1.08)	0.93 (0.82 – 0.97)	85
Knee extension L	1.0 (1.0 – 1.0)	0.97 (0.91 – 0.99)	90
Knee extension R	1.0 (1.0 – 1.0)	0.97 (0.92 – 0.99)	90
Ankle DF L	0.86 (0.58 – 1.13)	0.97 (0.93 – 0.99)	90
Ankle DF R	1.0 (1.0 – 1.0)	0.97 (0.94 – 0.99)	90

Kappa statistic using binary outcome of clinical weakness (Medical Research Council score <4; ≥4). n=20

Abbreviations: Abd = abduction. DF = dorsiflexion. L = left. R = right. CI = confidence interval. ICC = intra-class correlation coefficient.

Minimum, maximum and median scores for each clinician's individual muscle group score on simulated presentations are shown in Table 3-7. No significant difference between both clinicians' median scores for individual muscle groups was evident, and for two muscle groups (left shoulder abduction and left hip flexion) both sets of scores were identical.

Table 3-7 Individual muscle group scores for simulated weakness presentations

Muscle group	Rater 1			Rater 2			p value
	Min	Max	Median (IQR)	Min	Max	Median (IQR)	
Shoulder Abd L	1	5	4 (2-4)	1	5	4 (2-4)	---
Shoulder Abd R	1	5	4 (2.25-4)	1	5	4 (2.25-4)	1.0
Elbow flexion L	2	5	4 (3.25-4)	2	5	4 (4-4)	1.0
Elbow flexion R	2	5	4 (3-5)	2	5	4 (3-5)	1.0
Wrist extension L	1	5	4 (3-4)	1	5	4 (3.25-4)	0.35
Wrist extension R	2	5	4 (3-4.75)	2	5	4 (3-5)	1.0
Hip flexion L	2	5	4 (3-4)	2	5	4 (3-4)	---
Hip flexion R	2	5	4 (4-5)	2	5	4 (3-4.75)	0.15
Knee extension L	2	5	4 (2-4)	2	5	4 (2-5)	0.35
Knee extension R	2	5	4 (2-5)	2	5	4 (2-5)	0.35
Ankle DF L	1	5	4 (2.25-4)	1	5	4 (2.25-4)	1.0
Ankle DF R	1	5	4.5 (2.5-5)	1	5	4 (2.5-5)	1.0

p values derived from Wilcoxon signed rank test for equality of median score. --- = both clinicians' median scores identical therefore unable to compute result. n=20.

Abbreviations: Abd = abduction. DF = dorsiflexion. L = left. R = right. Min = minimum score. Max =maximum score. IQR = interquartile range.

Inter-observer agreement of each clinician's MRC-SS from simulated presentations was compared against the reference score. Both clinicians demonstrated an ICC of 1.0 (95% CI 1.0-1.0), percent agreements of 65 and 70% and perfect agreement for diagnosis of ICU-AW with Kappa statistics of 1.0 (95% CI 1.0-1.0). Table 3-8 and Table 3-9 report each clinician's individual muscle group scores against the reference MRC score. High levels of agreement were evident for both clinicians.

Table 3-8 Inter-observer agreement between Clinician 1 and reference scores for individual muscle groups

Muscle group	Kappa (95% CI)	ICC (95% CI)	% agreement
Shoulder Abd L	0.9 (0.71 – 1.09)	0.98 (0.95 – 0.99)	95
Shoulder Abd R	0.9 (0.7 – 1.09)	0.98 (0.95 – 0.99)	95
Elbow flexion L	0.86 (0.58 – 1.13)	0.96 (0.91 – 0.99)	95
Elbow flexion R	1.0 (1.0 – 1.0)	1.0 (1.0 – 1.0)	100
Wrist extension L	0.88 (0.64 – 1.11)	0.98 (0.94 – 0.99)	95
Wrist extension R	1.0 (1.0 – 1.0)	1.0 (1.0 – 1.0)	100
Hip flexion L	1.0 (1.0 – 1.0)	1.0 (1.0 – 1.0)	100
Hip flexion R	0.86 (0.58 – 1.13)	0.95 (0.88 – 0.98)	90
Knee extension L	1.0 (1.0 – 1.0)	0.97 (0.91 – 0.99)	90
Knee extension R	1.0 (1.0 – 1.0)	1.0 (1.0 – 1.0)	100
Ankle DF L	1.0 (1.0 – 1.0)	0.99 (0.97 – 0.99)	95
Ankle DF R	1.0 (1.0 – 1.0)	0.97 (0.94 – 0.99)	90

Kappa statistic using binary outcome of clinical weakness (Medical Research Council score <4;≥4).

Abbreviations: Abd = abduction. DF = dorsiflexion. L = left. R = right. CI = confidence interval. ICC = intra-class correlation coefficient

Table 3-9 Inter-observer agreement between Clinician 2 and reference scores for individual muscle groups

Muscle group	Kappa (95% CI)	ICC (95% CI)	% agreement
Shoulder Abd L	0.9 (0.71 – 1.09)	0.98 (0.95 – 0.99)	95
Shoulder Abd R	0.9 (0.7 – 1.09)	0.96 (0.89 – 0.98)	90
Elbow flexion L	1.0 (1.0 – 1.0)	1.0 (1.0-1.0)	100
Elbow flexion R	1.0 (1.0 – 1.0)	0.98 (0.94 – 0.99)	95
Wrist extension L	1.0 (1.0 – 1.0)	0.98 (0.94 – 0.99)	95
Wrist extension R	1.0 (1.0 – 1.0)	0.98 (0.95 – 0.99)	95
Hip flexion L	1.0 (1.0 – 1.0)	1.0 (1.0-1.0)	100
Hip flexion R	0.88 (0.64 – 1.11)	0.98 (0.94 – 0.99)	90
Knee extension L	1.0 (1.0 – 1.0)	1.0 (1.0-1.0)	100
Knee extension R	1.0 (1.0 – 1.0)	0.97 (0.92 – 0.99)	90
Ankle DF L	0.86 (0.58 – 1.13)	0.99 (0.97 – 1.0)	95
Ankle DF R	1.0 (1.0 – 1.0)	1.0 (1.0-1.0)	100

Kappa statistic using binary outcome of clinical weakness (Medical Research Council score <4;≥4).

Abbreviations: Abd = abduction. DF = dorsiflexion. L = left. R = right. CI = confidence interval. ICC = intra-class correlation coefficient

3.3.2 Study 2 - Clinical predictive value of the MRC-SS

3.3.2.1 Clinical predictive value for ability to perform MRC-SS testing at awakening

94 patients were eligible for enrolment in the 3-month study period (Figure 3-4). Baseline demographic data for the cohort are reported in Table 3-1. 18 patients died prior to any testing, and 11 patients were consistently unable to perform (UTP) MRC-SS testing throughout their ICU stay due to cognitive impairment. MRC-SS were obtained in 65 patients at awakening. Categorising the cohort into those patients able to perform (ATP) MRC-SS testing and those UTP at awakening, significant differences between groups were evident for age (ATP 35.3±14.9years vs. UTP 60.6±20.0years; $p<0.0001$), illness severity on ICU admission (APACHE II) (ATP 18.5±5.1 vs. UTP 14.9±4.6; $p=0.03$) and hospital length of stay (LOS) (ATP 33.0 (14.5-55.5) days vs. UTP 15.0 (7.0-37.0) days; $p=0.02$). Groups were similar for gender, ICU LOS and total mechanical ventilation (MV) days. Duration of MV prior to awakening MRC-SS was 5.0 (3.0-9.5) days in the ATP group, and following testing 0.0 (0.0-6.5) days. In the UTP group, number of attempted MRC-SS assessments was 4.0 (2.0-8.0). ICU mortality was 12.3% and 0.0%, and hospital mortality 24.6% and 18.2%, for ATP and UTP groups, respectively.

Fisher's exact testing was performed to examine any association between ability to perform the test at awakening and ICU and hospital mortality and LOS. All tests were non-significant and therefore further analysis of test characteristics was not considered appropriate (Table 3-10).

At Day 7, 45 of the 65 patients with awakening scores had been discharged from the ICU (8 patients had died, 37 patients transferred to the ward or repatriated) and a further 6 were unable to perform the test. MRC-SS for the 14 patients with scores at this time-point was 33.5 (22.3-44.8). 11 patients had ICU-AW (MRC-SS <48/60). Due to the small numbers, further analysis on this cohort was not considered appropriate.

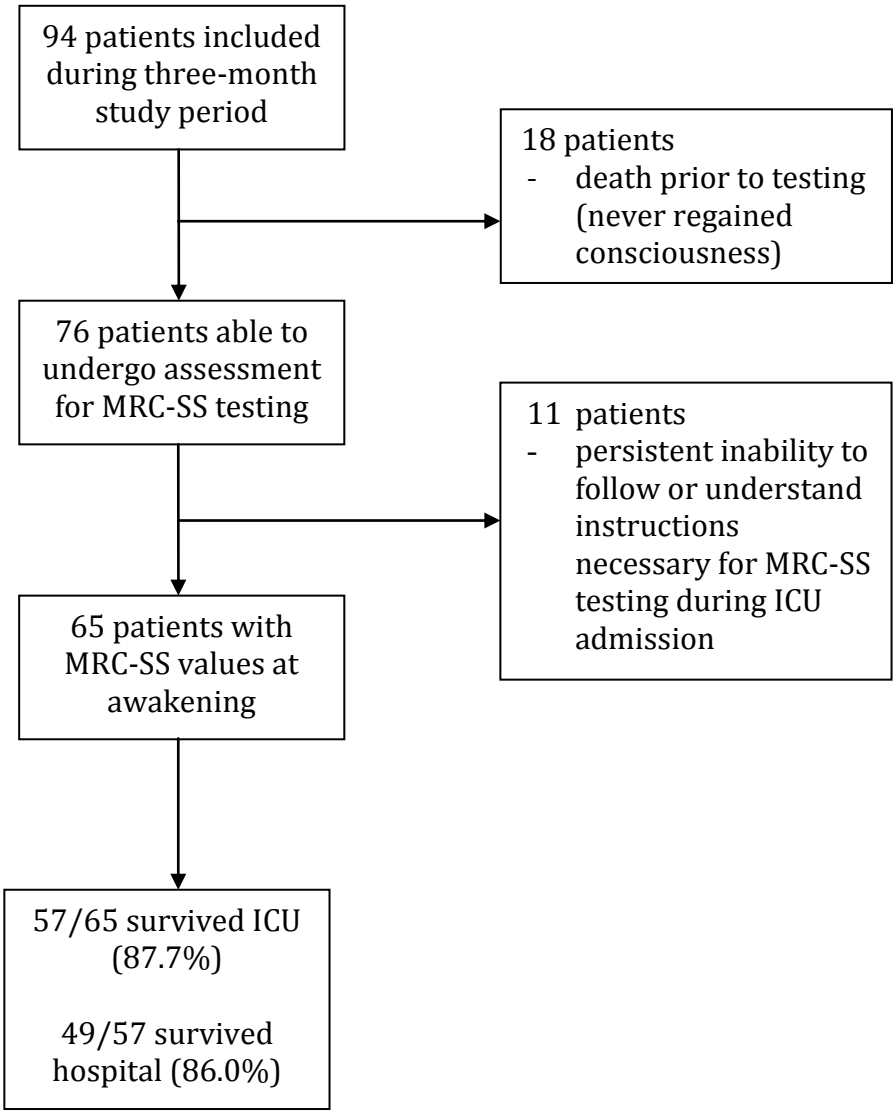


Figure 3-4 Flow diagram of patient enrolment in study

Abbreviations: MRC-SS = Medical Research Council sum-score; ICU = Intensive Care Unit

Table 3-10 2x2 contingency tables for ability to perform MRC-SS testing at awakening

		ICU mortality	
		Deceased	**Alive**
MRC-SS performance status	**UTP**	0	11
	ATP	8	57

		Hospital mortality	
		Deceased	**Alive**
MRC-SS performance status	**UTP**	2	9
	ATP	16	49

		ICU LOS	
		>14 days	**≤14 days**
MRC-SS performance status	**UTP**	3	8
	ATP	28	37

		Hospital LOS	
		>28 days	**≤28 days**
MRC-SS performance status	**UTP**	4	7
	ATP	38	27

p values calculated using Fisher's exact test. n=76.
ICU mortality, p=0.59; Hospital mortality, p=1.0; ICU LOS, p=0.51; Hospital LOS, p=0.20.

Abbreviations: MRC-SS = Medical Research Council sum-score. UTP = unable to perform. ATP = able to perform. LOS = length of stay.

3.3.2.2 Clinical predictive value of an MRC-SS <48 and ≥48 at awakening

Sixty-five patients had MRC-SS at awakening; 33 with scores of 0-36 (50.8%), 15 (23.1%) scored 37-47, and 17 (26.1%) ≥48. Prevalence of ICU-AW (MRC-SS <48) in the cohort was 73.9% (M:F 35:13). When these scores were examined in detail, there was no pattern indicating a trend of proximal-distal distribution of muscle group weakness, nor any consistent symmetry to the weakness presentation.

There was no association between MRC-SS and ICU and hospital mortality demonstrated (p=0.67 and p=0.53, respectively) and therefore further analysis of test characteristics was not performed. However a significant association was found for ICU and hospital LOS (p=0.004 and p=0.04, respectively (Table 3-11). The clinical predictive value of MRC-SS <48 at awakening was therefore determined (Table 3-12). Using a cut-off of 75%, high sensitivity was evident for ICU and hospital LOS. Specificity and PPV were poor across both, and high NPV was evident for ICU LOS.

In addition, receiver-operator characteristic (ROC) analysis was performed on the 65 awakening MRC-SS measurements for each clinical outcome (ICU and hospital mortality, and ICU and hospital LOS) to assess sensitivity and specificity at levels of MRC-SS from zero to 60 (Table 3-13). Greatest sensitivity was observed at an MRC-SS <35 (64.3%) with 64.9% specificity (area under curve (AUC) 0.69 (95%CI 0.56-0.82)) for ICU LOS, and greatest specificity was observed at an MRC-SS <29.5 (70.2%) with sensitivity of 62.5% (AUC 0.63 (95%CI 0.42-0.83)) for ICU mortality.

Table 3-11 2x2 contingency tables for MRC-SS <48 at awakening

		ICU mortality	
		Deceased	**Alive**
MRC-SS performance status	**<48**	7	41
	≥48	1	16

		Hospital mortality	
		Deceased	**Alive**
MRC-SS performance status	**<48**	13	35
	≥48	3	14

		ICU LOS	
		>14 days	**≤14 days**
MRC-SS performance status	**<48**	26	22
	≥48	2	15

		Hospital LOS	
		>28 days	**≤28 days**
MRC-SS performance status	**<48**	32	16
	≥48	6	11

p values calculated using Fisher's exact test. n=65.
ICU mortality, p=0.67; Hospital mortality, p=0.53; ICU LOS, p=0.004; Hospital LOS, p=0.04.

Abbreviations: MRC-SS = Medical Research Council sum-score (scored/60). UTP = unable to perform. ATP = able to perform. LOS = length of stay.

Table 3-12 Clinical predictive value of an MRC-SS <48/60 at awakening

	ICU LOS (≤14 days and >14days)		Hospital LOS (≤28 days and >28 days)	
	%	**95% CI**	**%**	**95% CI**
Sensitivity	92.9	76.5-99.1	84.2	68.7-94.0
Specificity	40.5	24.8-57.9	40.7	22.4-61.2
PPV	54.2	39.2-68.6	66.7	51.6-79.6
NPV	88.2	63.6-98.5	64.7	38.3-85.8

Abbreviations: ICU = intensive care unit. LOS = length of stay. PPV = positive predictive value. NPV = negative predictive value. CI = confidence intervals.

Table 3-13 Receiver-operator curve analyses of MRC-SS at awakening and clinical outcome

Clinical outcome	MRC-SS (/60)	Sensitivity (%)	Specificity (%)	AUC (95%CI)	p value
ICU mortality	<29.5	62.5	70.2	0.63 (0.42-0.83)	0.3
ICU LOS	<35	64.3	64.9	0.69 (0.56-0.82)	0.009
Hospital mortality	<35	62.5	57.1	0.55 (0.4-0.7)	0.6
Hospital LOS	<36.5	60.5	63.0	0.65 (0.51-0.79)	0.04

n=65. Cut-offs reported represent those at which greatest levels of sensitivity and specificity were identified.

Abbreviations: MRC-SS = Medical Research Council sum score. ICU = Intensive Care Unit. LOS = length of stay. AUC = area under the curve. CI = confidence interval.

3.3.2.3 Relationship between MRC-SS at awakening and handgrip strength and physical function at ICU discharge

MRC-SS at awakening demonstrated significant positive correlations with Barthel scale (r=0.4, p=0.005), EMS (r=0.4, p=0.005), and bilateral handgrip strength (left (r=0.5, p=0.0003), right (r=0.5, p<0.0001)) performed at ICU discharge (Figure 3-5). Measures of physical function and handgrip strength were also compared according to diagnosis of ICU-AW (MRC-SS <48/60; ≥48/60) (Table 3-14). Significant differences were evident between groups for left (p=0.04) and right (p=0.002) handgrip strength. Furthermore handgrip strength values at ICU discharge for those patients with ICU-AW at awakening were consistent with a diagnosis of ICU-AW according to previously reported handgrip cut-offs [36]. Differences for Barthel and EMS scores approached significance.

Table 3-14 MRC-SS at awakening and measures of handgrip strength and physical function at intensive care unit discharge

	MRC-SS <48 (n=48)	MRC-SS ≥48 (n=17)	p value
L HGD (kg)	7.0 (2.0-15.0)	12.0 (9.0-24.0)	0.02
R HGD (kg)	7.0 (2-13.5)	16.0 (11.0-25.0)	0.002
Barthel score (/20)	2.0 (0-8.5)	8.0 (1.0-11.0)	0.05
EMS (/20)	2.0 (0.0-8.0)	6.0 (2.0-15.0)	0.07

Data are presented as median (interquartile range). p values derived from Mann-Whitney analysis. For Barthel and EMS, higher score indicate a better level of physical function.

Abbreviations: MRC-SS = Medical Research Council Sum-score. EMS = Elderly Mobility Scale. L = left. R = right. HGD = handgrip dynamometry.

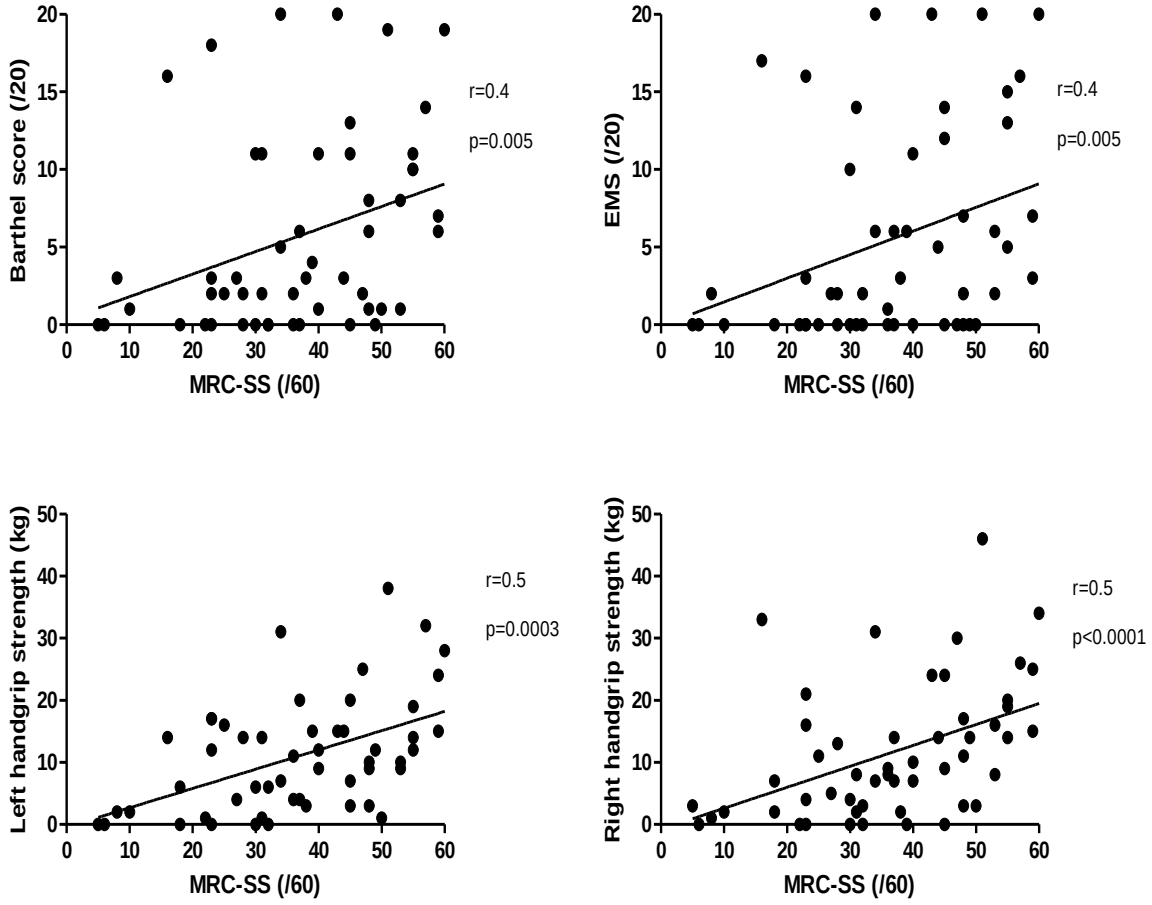


Figure 3-5 Relationship between MRC-SS at awakening and measures of physical function on ICU discharge

p and r values derived from Spearman's correlation coefficient. n=52

Abbreviations: MRC-SS = Medical Research Council Sum-score. ICU = intensive care unit. EMS = Elderly Mobility Scale.

3.4 Discussion

Data from the current study demonstrate high levels of inter-observer agreement between two expert clinicians assessing both ICU patients and simulated presentations of weakness, but only moderate agreement was observed for the diagnosis of ICU-AW in the clinical ICU patient cohort. The inter-observer agreement using the MRC-SS to diagnose ICU-AW was therefore an effect of patient variability rather than clinician variability during assessment, and is not unexpected due to the volitional nature of the test. At awakening, almost one third of patients were unable to complete MRC-SS testing, but there was no relationship between the ability to perform the MRC-SS at awakening and ICU and hospital mortality or length of stay. Similarly there was no association found between an MRC-SS <48/60 at awakening, considered as the diagnostic 'cut-off' for ICU-AW, and ICU or hospital mortality. Furthermore, whilst a significant association was evident for ICU and hospital length of stay, further test characteristic analysis revealed limited positive predictive value for both, and a high negative predictive value for an ICU length of stay of more than 2 weeks. Clinically, this confirms that a diagnosis of ICU-AW based on an MRC-SS <48/60 had poor predictive value, whereas an MRC-SS greater than 48 predicted a more favourable outcome albeit only in relation to the specific outcomes assessed. Finally, only moderate correlations were evident between MRC-SS and two measures of physical function, and diagnosis of ICU-AW had limited clinical relevance in terms of physical function in ICU survivors. These data highlight the limitation and clinical utility of the MRC-SS for diagnosing ICU-AW and its predictive consequences.

3.4.1 Critique of the method

3.4.1.1 Inter-observer agreement

Determining the ideal protocol for establishing inter-observer agreement of the MRC-SS in critically ill patients within ICU and controlling for potentially confounding variables is challenging. Patient testing was separated by 30 minutes to minimise effect of clinical fluctuation and limit patient exhaustion, albeit a greater duration may have been required for this purpose and specific assessment

of fatigability was not conducted to ensure this was not the case. Conversely, it could be argued that extending the time interval between each clinician's testing offers greater opportunity for alteration in patient clinical status that may negatively influence reliability in itself.

Whilst the inter-observer cohort studied could be considered relatively small (n=20) which limits generalisability of the findings, it is within the range of sample sizes previously reported in similar studies [59, 60, 244]. Furthermore, the cohort included a range of illness acuity, duration of ICU stay and requirements for mechanical ventilation. In addition nearly half of the patients had endotracheal tubes *in situ* at the time of testing. Despite clinical status, all patients were screened as suitably awake and cognitively intact to proceed with assessment. For this reason, manual muscle testing will exclude those patients in the early stages of critical illness when the patient is likely to have impaired cognition due to high sedation load, septic or metabolic encephalopathy, or neurological deficit [38]. Actual testing occurred at various points within each patient's ICU admission, which could have affected reliability. Performing assessments at a standardised time-point may offer further insight into the usefulness and reliability of the measure, and comparison between patient groups.

A standardised protocol for MRC-SS measurement was adopted for testing according to patient position to limit clinician variability, a strategy previously reported in only one other recent study [38], and the process for screening for level of awakening and alertness, and ability to undergo testing has been widely reported in the literature [11, 36, 37, 60]. However, despite these approaches it is acknowledged that patient-related factors may have influenced ability to perform the assessment irrespective of successfully meeting screening criteria on each occasion. Intervening clinical events, such as administration of sedation, could have attributed to this but were not documented.

3.4.1.2 Predictive value of the MRC-SS

Predictive value and test characteristics of the MRC-SS have not been investigated previously, but as a diagnostic test for ICU-AW this evaluation is warranted.

Clinical outcomes of mortality and length of stay were selected based on findings from previous observational cohort studies investigating ICU-AW, diagnosed using the MRC-SS (cut-off of <48/60 indicative of a positive test result) and clinical course [11, 36, 37]. However these outcomes are influenced by multiple factors in critically ill patients and peripheral muscle strength may not represent the most relevant diagnostic tool. Furthermore, only one-quarter of patients with an awakening MRC-SS value did not have ICU-AW, and hence these data require careful interpretation.

A proportion of the cohort were unable to complete MRC-SS testing due to persistent inability to understand or follow the necessary instructions, suggesting screening using simple one-stage commands may be inadequately sensitive to detect cognitive ability sufficient for MRC-SS assessment. More thorough assessment of delirium and complex cognitive ability may have addressed this [245], but the study aimed to reflect the common approach employed previously [11, 36, 37, 60].

In the current study, awakening was defined as the first occasion on which an MRC-SS could be obtained from a patient. This was in contrast to the landmark study of De Jonghe *et al* [11], who defined ICU-AW as an MRC-SS less than 48 at seven days post awakening. Whilst this definition ensured that the weakness detected was persistent, and not a fluctuating finding in the early stages of patient waking, in the current patient cohort due to high rates of patient discharge from the ICU by day 7, scores at this time were considerably less useful. Specifically, the majority of patients in the ICU at day 7 post awakening demonstrated ICU-AW, but this was a small subgroup of the general ICU patient cohort studied (15%) and analysis of these data were extremely limited. It is likely these findings represent, in part, an overall change in clinical ICU practice toward earlier discharge as a result of implementation of structured weaning and reduced-sedation protocols, and a growing culture of early mobilisation.

3.4.1.3 MRC-SS and physical function and handgrip strength

There are few recognised, validated outcome measures for critically ill patients on discharge from the ICU. Two measures were selected that represented a range of physical functional activities potentially requiring rehabilitation intervention following ICU discharge, albeit these measures originated from different patient populations [235, 241]. Only moderate correlations were demonstrated with the MRC-SS, which could be a result of the poor validity of these measures in the post ICU population, rather than a function of the MRC-SS as a measure. Furthermore, MRC-SS and physical function were measured at differing time-points, at awakening and within 72 hours of ICU discharge respectively. The latter time frame was adopted for clinical reasons (to ensure patient stability on transfer to the ward and for undergoing assessment) and pragmatic reasons (to enable one assessing clinician to be available for testing) reasons. However global clinical improvement in the interim period may have influenced the relationship observed. Contemporaneous measurements of MRC-SS and physical function may have yielded stronger correlations, but physical function manoeuvres are generally not possible at awakening and MRC-SS measurements beyond awakening limit use of the score as a predictor of both ICU and hospital outcome.

3.4.2 Clinical interpretation

3.4.2.1 Inter-observer agreement

Although inter-observer agreement was determined in a small sample of ICU patients recovering from critical illness, this allowed testing in a relatively stable group of patients with potentially less clinical fluctuation, whilst still in the ICU. Patients demonstrated a range of ICU length of stay. However, overall only moderate agreement for MRC-SS less than 48, diagnostic of ICU-AW, was evident, with wide confidence intervals including both poor and almost perfect agreement due to sample size and prevalence of weakness. For simulated weakness presentations, levels of agreement between clinicians were completely matched for the value of MRC-SS and diagnosing ICU-AW. These data strongly support the conclusion that inter-observer variability was the result of patient-related

variation in ability to perform the volitional MRC-SS, rather than variability between clinicians in performing the assessment. Whilst previously assumed, these results confirm this source of error in determining inter-observer agreement of MRC-SS measurement, and represent an important and novel aspect of the current study.

Inter-observer agreement of the MRC-SS was examined, rather than intra-observer or repeated assessment, given that in routine clinical practice it is likely that more than one therapist would be involved in management of critically ill patients, and any potentially diagnostic measure requires consistency between clinicians. In order to examine the optimum potential agreement that could be observed, experienced raters were employed to reduced bias. However it is also acknowledged that clinicians with varying experience may be involved in patient care, and demonstrate greater variability in scoring. Data have been reported suggesting that with adequate training, novices may demonstrate good reliability compared with an expert reference, although the patient cohort in question was a combination of simulated weakness and patients post ICU in stable recovery phase [59].

That only moderate agreement was evident between clinicians for the diagnosis of ICU-AW may have an impact on the delivery of therapeutic rehabilitation interventions, assuming those presenting with ICU-AW would have the greatest requirement and be most likely to benefit. Furthermore, lack of strong agreement restricts clinicians' ability to accurately monitor patient progress during recovery.

3.4.2.2 Predictive value of the MRC-SS

Although previous data have associated ICU-AW with poor clinical outcome [11, 36, 37, 40], determining the test characteristics of the MRC-SS as an assessment tool has never previously been reported in the literature. Hence the clinical interpretation of these data is significant. Inability to perform the test did not predict a poor outcome in terms of ICU and hospital mortality and length of stay; indeed there was no association between ability to perform the test and these clinical outcomes and thus rendering calculation of test characteristics unfeasible.

Likewise, there was no relationship observed between preserved peripheral muscle strength (MRC-SS >48) and ICU-AW (MRC-SS ≤48) and mortality. Despite an association being demonstrated between MRC-SS and ICU and hospital length of stay, test characteristics revealed that whilst higher scores predicted favourable outcome, lower scores did not predict a poor clinical outcome. That sensitivity was high for both ICU and hospital length of stay is of limited clinical relevance in this scenario. Positive and negative predictive values are the properties that enable to judgement to be made prospectively on a patient's outcome based on their presentation on assessment at awakening.

In essence ability to perform the test and consequently scoring highly, were able to indicate a more favourable outcome in terms of ICU and hospital length of stay. However, 'negative' test status i.e. either inability to perform the test or scoring ≤48/60 provided no predictive value of outcome. These observations are, in principle, similar to those made when using volitional measurements of respiratory muscle strength, whereby a high value supports confirmation of preserved muscle strength, but a low value is not necessarily representative of muscle weakness, but related to ability to perform the test effectively [246-249]. In addition further analysis using receiver operator curves to define an MRC-SS cut-off for each of the important clinical outcomes of ICU and hospital mortality and length of stay failed to identify clinically meaningful values of the MRC-SS.

These data highlight the limitations in the robustness of the MRC-SS for use in day-to-day clinical practice for considering outcome, albeit the sample size in this study is likely to be too small to be definitive and the confidence intervals around all test characteristic values are wide. Alternative outcome measures are required for monitoring the progression of muscle wasting and weakness in critically ill patients, which need to be correlated with physical performance. Recent data has demonstrated a reduction in quadriceps rectus femoris cross sectional area during early critical illness measured using ultrasound [250] with muscle layer thickness negatively correlated with length of stay [82]. These simple non-volitional and effort-independent tests have the potential for further clinical application in the intensive care unit to provide more physiologically accurate and robust data on muscle structure and function during critical illness.

3.4.2.3 MRC-SS and physical function

Patients diagnosed with ICU-AW demonstrated reduced handgrip strength compared to those without ICU-AW, which is similar to previously reported data [36]. However, the current data only demonstrated a moderate direct relationship between MRC-SS at awakening and handgrip strength at ICU discharge which is not wholly unexpected. This is in part a consequence of both the different timings of assessment as well as the different muscle groups that are assessed during each test. MRC-SS testing does not include distal muscle function, such as hand muscle strength, a muscle group often affected early on as part of a motor neuropathy [5]. Furthermore, ability to perform handgrip dynamometry according to standard guidelines [233] requires upper limb strength and thus upper limb weakness demonstrated by those patients with MRC-SS less than 48 would have been expected to influence performance of this measure. Data regarding hand dominance was not recorded and hence it is not possible to comment on the influence of this on the current results.

Only a moderate correlation was shown between MRC-SS and two common measures of physical function, which again is not unexpected given these represent different domains of muscle impairment and function. In addition to the different timings of the assessments, the MRC-SS is a composite score of peripheral muscle strength, based on single muscle group manoeuvres. It fails to capture the spectrum of complex motor tasks and interaction between skeletal muscle strength and endurance, balance, co-ordination and higher-level cognition required for complex physical function activities. Many activities assessed with the Barthel and EMS scales involve hand function, not measured by MRC-SS testing. It was not possible to assess physical function at awakening and testing MRC-SS at discharge was not central to the current study, which focussed on the usefulness of MRC-SS testing during the early stage of critical illness. Furthermore there was no difference in physical function measures between groups with and without a diagnosis of ICU-AW, albeit this may be attributable to the smaller sample of patients without ICU-AW following ICU discharge and p values approached statistical significance. Nonetheless these findings suggest that using the MRC-SS to grade strength in critically ill patients may not accurately reflect

level of physical functional ability, which has implications for provision of targeted rehabilitation interventions.

3.4.3 Comparison with previous studies

3.4.3.1 Inter-observer agreement

In addition to the current dataset inter-observer agreement for manual muscle testing using the MRC-SS in critically ill patients has been reported by a small number of previous authors. In a minor subset of their main critically ill patient cohort (n=12, out of 174), Ali *et al* [36] reported complete agreement between two examiners for diagnosing ICU-AW. It is unclear, however, at which time point during admission these assessments were performed to enable comparison. Further high Kappa agreement values of 88% for diagnosing ICU-AW have also been demonstrated, albeit in a combined cohort (n=19) of simulated and stable, recovery-stage patients post ICU-discharge [59]. The earliest data on agreement documented on ICU patients assessed whilst *within* the ICU came from a cohort studied by Hough *et al* in 2011 [60] where only 10 patients were able to undergo testing, and only modest agreement for scoring MRC-SS <48/60 was evident (Kappa 0.38). Agreement in patients assessed following ICU discharge was complete (Kappa 1.0). In a larger cohort of 75 ICU patients, a third of whom were long-stay admissions of ≥15 days, agreement for identifying patients with MRC-SS <48/60 was moderate to good (Kappa 0.68±0.09). For identifying severe weakness i.e. MRC-SS <36/60 agreement was almost complete (0.93±0.07).

These contrasting datasets challenge the clinical usefulness of using the MRC-SS to measure ICU-AW in patients within the ICU and early in their critical illness. Although original reports of MRC-SS testing by Kleyweg *et al* [35] demonstrated high levels of inter-observer reliability of the MRC-SS, this was in a cohort of recovering stable patients with Guillain-Barré syndrome, albeit the cohort included bedbound patients still requiring invasive ventilatory support. Inherent clinical variation and unpredictability during early critical illness highlight the major limitations of employing volitional testing in this population thus affecting reliability. Agreement is poorer in patients within the ICU compared to those more

stable patients following ICU discharge, or where simulated weakness is utilised as a comparator as in the current study. Furthermore levels of disagreement within the ICU are influenced by the construct of the MRC grading scale itself, such that levels 3 and below which are objective to score, demonstrate strongest agreement, and levels 4 and above, involving arbitrary levels of applied resistance are more challenging. Thus, as mentioned previously, disagreement centres on patient-related variability in turn compounded by the nature of the score itself.

In addition to the MRC-SS, Vanpee *et al* [244] examined inter-observer agreement of handheld dynamometry, an alternative form of manual muscle testing. In their cohort of 39 critically ill patients, Vanpee and colleagues reported good levels of agreement in the six muscle groups comprising the MRC-SS (ICC ranging 0.76-0.96). However testing was restricted to only those awake and cooperative patients, scoring >3 on the MRC scale i.e. movement against gravity. These findings were echoed by Baldwin *et al* [50] who reported good levels of inter-rater reliability across handgrip, elbow flexion and knee extension dynamometry, although it was noted that improvements of approximately 20% would be required to reflect real force changes in critically ill patients.

In contrast to previous reports, we found no pattern in distribution of weakness of either a proximal-to-distal nature, or regarding symmetry. However dominance was not recorded to examine if this was a contributing factor, nor presence of specific lines, attachments or other similar monitoring device at the time of testing that may have accounted for individual variation in particular muscle group scores.

3.4.3.2 Predictive value of the MRC-SS

Whilst many observational studies have shown associations between ICU-AW and both short-term and long-term outcomes, including mortality and length of stay [11, 36, 37, 43], surprisingly there have been no previous data reported investigating the test characteristics of the MRC-SS for these important clinical outcomes. Given its role as a diagnostic tool for ICU-AW such analysis is warranted, and the current study provides novel data in an attempt to address this,

presenting unique findings that challenge the usefulness of the MRC-SS for predicting outcome in critically ill patients.

In the present cohort a proportion of patients never regained conscious to undergo testing. This is in keeping with a number of other reports and highlights the challenging feasibility of the MRC-SS in the ICU population [11, 36, 38, 60]. In such patients the usefulness or relevance of a diagnosis of ICU-AW is debatable, and whether any change in clinical course or management would be influenced by such a finding [60, 251]. However confirming muscle weakness or impairment at an early stage may alert clinicians to directing physical rehabilitation therapy or other medical strategies aimed at ameliorating muscle wasting and weakness, and thus potentially altering clinical outcome. Nonetheless it is important to understand and assess muscle strength, physical function and/or exercise capacity at ICU discharge in order to optimise ongoing rehabilitation input beyond the ICU.

3.4.3.3 Physical function and handgrip strength

Data from the current study demonstrating a significant difference between those patients with and without ICU-AW in terms of handgrip strength are in keeping with those previously reported [36]. Furthermore, in the study by Ali *et al* [36] gender-specific thresholds were identified for handgrip strength that could be used to identify ICU-AW. Whilst advantageous in that this would minimise the number of muscle groups requiring assessment for diagnosis, handgrip strength is limited by the same caveats associated with volitional measures..

However there are limited available data evaluating the relationship between ICU-AW and physical function. Whilst this was not the focus of the current study, follow-up of those patients with awakening MRC-SS values permitted some investigation of this. There was no difference in physical function characterised using two commonly implemented measures for hospital in-patients, between those patients with (MRC-SS <48/60) and without (MRC-SS ≥48/60) ICU-AW, although it is acknowledged that statistical significance was approached. These are similar to the findings from Kleyweg *et al's* original MRC-SS work [35] who reported that in patients with higher physical function levels, the MRC-SS offered

little additional information. One explanation for this change in MRC-SS without a change in functional level, is the lack of sensitivity in the MRC grading scale to diagnose clinical weakness despite the presence of underlying electrophysiological changes [27]. Further investigation of this concept is required in prospective studies with contemporaneous assessment points, but the current data suggests that MRC-SS may not be an accurate marker to predict physical function in critically ill patients. Indeed, level of physical function itself, may be more appropriate reflection of impairment in muscle function developed during critical illness, and be used to direct physical rehabilitation interventions.

3.4.4 Future studies

A number of methodological factors arising through the studies discussed in this chapter could be considered in order to enhance the conduct of future similar investigations. Whilst patients were assessed for awakening using widely reported screening criteria (categorisation on a known sedation scale and completion of simple, one-stage commands), it is acknowledged that a thorough assessment of confusion and delirium prior to testing would provide greater insight into patients' appropriateness to perform volitional manual muscle testing to an optimum capability. The Confusion Assessment Method for the ICU (CAM-ICU) [245] is a commonly reported technique for this purpose and undertaking such an assessment would add robustness to this stage of the protocol. In tandem with this, a future protocol should carefully consider timing of testing in relation to delivery of any sedation dose and any sedation hold performed. This is in itself would require clear definition, as practice in this area can vary between different clinicians and ICUs. Accurately capturing data on intervening pharmacotherapy between testing by both clinicians would ensure the clinical status of patients is fully characterised and that results could be interpreted fully in the context of the influence of any agents on reliability. These aspects particularly focussing on patient testing are significant as it is essentially intra- and inter-observer reliability and agreement in the patient population that is of most clinical importance, as opposed to that established in healthy subjects.

The current studies focussed on the MRC-SS cut off of less than 48 out of 60 as the diagnostic threshold for ICU-AW. Whilst we undertook preliminary analysis to identify any other cut-off levels with acceptable test characteristics, and found none that met suitable levels, further investigation could be warranted to examine this area in the critically ill population. Of particular interest would be to correlate levels of weakness with performance on physical functional tests in order to determine clinically important levels of weakness. In addition, the current studies found variability in precision of reliability and agreement in scores across different muscle groups. Future studies may benefit from examining performance of individual muscle groups in greater detail, as the current use of six functional upper and lower limb muscle groups may be in excess of requirements, especially in light of any relationships with physical function where certain muscle groups may be predominantly used.

3.5 Conclusion

The current data have identified the limitations of using the MRC-SS test to diagnose ICU-AW during the early stages of critical illness, which have important clinical considerations. Even when performed by expert clinicians, the fluctuating clinical status of patients significantly reduced inter-observer agreement of the test. Furthermore, inability to perform the test and a score indicative of ICU-AW demonstrated limited clinical usefulness in considering outcome. In addition, there was only a weak relationship between MRC-SS value and the level of physical function in ICU survivors. The findings of the current study reflect the inherent limitations of volitional strength testing in critically ill patients, in particular, in the early stages of the process. This strongly supports the need for alternative non-volitional techniques that can be applied to all patients, for objective assessment and monitoring of muscle wasting and weakness in critically ill patients.

Chapter 4 Quadriceps Rectus Femoris Cross-sectional area (RF_{CSA}): Relationship between Anatomical and Physiological RF_{CSA} and Quadriceps Strength

4.1 Introduction

Ultrasound has recently emerged as a potentially valuable and effective tool for measuring the changes in a variety of parameters detailing peripheral skeletal muscle structure during critical illness [81, 250, 252, 253]. It is an effort-independent technique that avoids ionising radiation, and it is quick, simple, cost-effective and easy to perform at the bedside. Furthermore it is widely accessible in the majority of intensive care units and, with basic training, can be implemented by a variety of non-specialist clinicians.

Characteristics of peripheral skeletal muscle that can be investigated using ultrasound include anatomical cross-sectional area (ACSA). One of the muscle groups commonly assessed is quadriceps rectus femoris as it is easily identifiable through its size and location [81-83, 86, 250, 252-254]. Previous data have reported a relationship between anatomical cross-sectional area of quadriceps rectus femoris (RF_{CSA}) and volitional and non-volitional measures of quadriceps muscle force in patients with chronic respiratory disease and healthy age-matched subjects [65, 73]. These data support the use of ultrasound in patient groups where accurate measurement of muscle force can be technically challenging, such as those with critical illness in the intensive care unit. Indeed, RF_{CSA} could act as a surrogate marker for muscle strength. In these studies RF_{CSA} was measured at a point three-fifths distance from the anterior superior iliac spine to the superior patellar border (3/5 distance). The anthropomorphic presentation of patients with chronic disease, often with disease-related skeletal muscle wasting, cachectic body composition and age-related muscle changes, is such that complete visualisation of RF_{CSA} is technically feasible at this measurement point. In the critically ill population, including younger patients without chronic co-morbidity or preceding muscle decline, this may not always be possible due to the current technical limitations of the device and the whole RF_{CSA} image is outside the scanning window of the probe. In these cases a more distal measurement point such as two-thirds distance from the anterior superior iliac spine (2/3 distance) allows entire RF_{CSA} image acquisition as muscle dimensions are smaller due the natural shape of the rectus femoris muscle as it extends towards insertion on the patella [82, 250]. This measurement point has also successfully been used to

determine muscle layer thickness in patients in the ICU [82]. However a relationship between RF_{CSA} measured at the 'two-thirds distance' measurement point and quadriceps force has not been previously confirmed.

In addition, in clinical research there has been little attention focussed on pennation angle, the angle of muscle fibre insertion [98], which can also be assessed using ultrasound. Measurement of pennation angle permits calculation of the physiological cross-sectional area (PCSA) of a muscle. This combination of anatomical cross-sectional area and fibre angle of the muscle allow both the size and the mechanical contractile properties of the muscle to be assessed. Physiological cross-sectional area could be hypothesised to demonstrate a stronger correlation with muscle strength [98], which may be clinically useful when considering use of this measurement in critically ill patients. However this has not been tested. Finally, there are few data reporting intra- and inter-observer reliability for use of ultrasound for the measurement of muscle size. Demonstrating acceptable levels of agreement of the technique would further support its use in the clinical setting.

4.1.1 Aims of study

The aims of this study were threefold:

1. To determine the relationship between RF_{CSA} measured at 2/3 distance, and volitional and non-volitional assessments of quadriceps force
2. To investigate the relationship between quadriceps rectus femoris physiological cross-sectional area (RF_{PCSA}), measured at both 3/5 and 2/3 distance, and volitional and non-volitional assessments of quadriceps force
3. To establish intra- and inter-observer agreement for measurement of RF_{CSA}.

4.2 Methods

4.2.1 Study design

This was a two-part, single-centre observational study. Study 1 investigated the relationship between RF_{CSA} and RF_{PCSA}, and volitional and non-volitional measurement of quadriceps force (quadriceps maximum voluntary contraction (QMVC), and twitch tension, (TwQ) respectively) in healthy subjects. Study 2 determined intra- and inter-observer agreement of ultrasound measurement of RF_{CSA}.

4.2.2 Participants

Healthy adult volunteers (≥18years of age) were eligible for inclusion for Study 1. Exclusion criteria included musculoskeletal pathology precluding ability to perform maximum voluntary quadriceps contractions. Pregnancy, presence of cardiac devices, and metal implants in the field excluded participation as documented contraindications to magnetic stimulation.

For Study 2, intra-observer agreement was investigated in a cohort of healthy subjects, and inter-observer agreement was investigated in critically ill adult patients (≥18years of age), all of whom were participating in existing research studies.

4.2.3 Measurements

4.2.3.1 Quadriceps rectus femoris anatomical cross-sectional area and pennation angle

Quadriceps rectus femoris anatomical cross-sectional area (RF_{CSA}) and pennation angle (RF_{PA}) were measured with real-time B-mode ultrasonography using an 8MHz 5.6cm linear transducer (PLM805, Toshiba Medical Systems Ltd, Crawley, UK) in keeping with previously described techniques [73, 95]. Measurements were taken at two-thirds (2/3 distance) and three-fifths (3/5 distance) distances

from the anterior superior iliac spine to the superior patellar border. Further detail for this technique is described in *Chapter 2.7.1*.

4.2.3.2 Quadriceps rectus femoris physiological cross-sectional area

Quadriceps rectus femoris physiological cross-sectional area (RF_{PCSA}) was calculated using the following equation,

$$RF_{PCSA}(cm^2) = RF_{CSA}(cm^2)\cos\theta$$

where θ is pennation angle [94, 98], and cosine of pennation angle normalises fibre angulation to the line of action of the muscle [99]. Physiological cross-sectional area is discussed in greater detail in *Chapter 1.5.2.1.*

4.2.3.3 Quadriceps maximum voluntary contraction and twitch tension

Strength was measured volitionally using the technique of isometric quadriceps maximum voluntary contraction, and non-volitionally using twitch tension following femoral nerve magnetic stimulation. Equipment set-up using a purpose-built strength-testing bench system was employed [74]. These techniques are described in further detail in *Chapter 2.6.1*.

4.2.3.4 Anthropometric measurements

Height, weight and fat-free mass were determined using bio-electrical impedance analysis (Bodystat® 1500, Bodystat®, Isle of Man, UK) (*Chapter 2.8*).

4.2.4 Study 1 – Relationship between anatomical and physiological quadriceps rectus femoris cross-sectional area and strength

Healthy subjects underwent ultrasound measurement of RF_{CSA} and RF_{PA} at both measurement points, volitional and non-volitional measurement of quadriceps force (QMVC and TwQ), and anthropometrics, on a single occasion.

4.2.5 Study 2 – Intra- and inter-observer agreement for use of ultrasound to measure quadriceps rectus femoris anatomical cross-sectional area

Healthy subjects underwent repeated measurements of RF_{CSA} separated by one hour (by the researcher, BC). Critically ill patients either within the ICU, or within twenty-fours of ICU discharge, underwent ultrasound measurement of RF_{CSA} by two experienced clinicians (BC and colleague). Measurements were performed independently and in a random order within 15minutes of each other.

4.2.6 Statistical analysis

For Study 1, unmatched group analysis of gender-specific quadriceps muscle force and cross-sectional data was performed using either unpaired or Mann-Whitney testing. Subsequent correlation testing determined the relationship between the variables of quadriceps muscle force and cross-sectional area.

In Study 2, inter-observer agreement between both clinicians for measurements of RF_{CSA} was determined using intra-class correlation coefficients (ICC) calculated using a two-way random effects for absolute agreement [242], and Bland-Altman analysis. This process was conducted for the whole set of measurements, and repeated according to specific measurement point i.e. 2/3 or 3/5 distances.

4.3 Results

4.3.1 Study 1 - Relationship between anatomical and physiological quadriceps rectus femoris cross-sectional area and strength

Twenty-one healthy adults participated. Ultrasound measurements of RF_{CSA} and RF_{PA} at 3/5 and 2/3 distances were obtained from all subjects. QMVC and TwQ were not obtained in one subject due to equipment failure, and TwQ in one further subject who was unable to tolerate magnetic stimulation. Anthropometric measures were obtained in all subjects. Baseline characteristics of the group are summarised in Table 4-1.

Table 4-1 Demographic and anthropometric data for the cohort

Characteristic	Value
Age (years)	31.0 (24.5-37.0)
Gender (M:F)	9:12
Height (m)	1.7±0.1
Weight (kg)	68.5±10.8
BMI (kg/m^2)	23.7±2.3
FFM (%)	77.1±8.6
Thigh length (cm)	45.0±2.5

Data are presented as mean±SD or median (interquartile range) as appropriate. Thigh length is the distance from the anterior superior iliac spine to superior patellar border.

Abbreviations: BMI = body mass index. FFM = fat-free mass.

Combined, and gender-specific, data for quadriceps strength and size are presented in Table 4-2. In all measures, with the exception of pennation angle and % activation, a significant difference between males and females was evident. There was no significant correlation found between pennation angle at either 3/5 or 2/3 distances, or anthropometric measures of age, height, weight, BMI, FFM or thigh length when data for both genders were analysed in combination. Analysis separating for gender also revealed no clinically relevant findings. Significant differences were evident between measures of force/unit area at each measurement point (3/5 vs. 2/3 distances, TwQ/RF_{CSA} 11.8±5.4g/mm^2 vs. 16.3±7.9g/mm^2, QMVC/RF_{CSA} 59.6±18.1g/mm^2 vs. 81.9±25.6g/mm^2, TwQ/RF_{PCSA} 12.0±5.4g/mm^2 vs. 16.5±8.0g/mm^2, QMVC/RF_{PCSA} 60.7±18.5g/mm^2 vs. 83.0±26.0g/mm^2, all $p<0.0001$).

Table 4-2 Quadriceps muscle strength and architecture data for healthy subjects

Measurement	Combined (n=21)	Males (n=9)	Females (n=12)	p value
QMVC (kg)	44.8±12.0	55.2±7.1	36.3±7.5	<0.0001
TwQ (kg)	9.6±4.0	12.6±3.6	7.4±2.5	0.0002
% activation	85.5±9.5	83.9±9.3	86.9±9.8	0.5
3/5 RF_{CSA} (mm^2)	720.6±206.7	891.9±167.7	592.1±123.4	0.0001
3/5 RF_{PA} (°)	10.4 (9.8-11.5)	10.3 (9.7-10.7)	10.8 (9.8-12.1)	0.4*
3/5 RF_{PCSA} (mm^2)	708.1±204.3	877.2±166.2	581.2±121.6	0.0001
2/3 RF_{CSA} (mm^2)	520.7±148.2	627.2±111.8	440.9±120.9	0.002
2/3 RF_{PA}(°)	8.8 (8.3-9.6)	8.8 (8.2-10.9)	8.8 (8.4-9.4)	0.8*
2/3 RF_{PCSA} (mm^2)	513.7±145.5	618.3±108.8	435.3±119.3	0.002

Data are presented as mean±SD or median (interquartile range) as appropriate. p values derived from unpaired *t* tests, or Mann-Whitney test (indicated by *) and compare M:F.
TwQ males, n=8; QMVC, TwQ, TwQ females, n=10.

Abbreviations: QMVC = quadriceps maximum voluntary contraction. TwQ = quadriceps twitch force. RF_{CSA} = rectus femoris cross-sectional area. RF_{PA} = rectus femoris pennation angle. RF_{PCSA} = rectus femoris physiological cross-sectional area. 3/5 = three-fifths distance from anterior superior iliac spine to superior patellar border. 2/3 = two-thirds distance from anterior superior iliac spine to superior patellar border.

Quadriceps strength showed a linear relationship with RF_{CSA} (vs. QMVC, r=0.7, p=0.001 and vs. TwQ, r=0.7, p=0.001) and RF_{PCSA} (vs. QMVC, r=0.7, p=0.001, and vs. TwQ, r=0.7, p=0.001) at 3/5 distance as shown in Figure 4-1. Figure 4-2 shows the relationship was similar at 2/3 distance - RF_{CSA} (vs. QMVC, r=0.6, p=0.002 and vs. TwQ, r=0.6, p=0.01) and RF_{PCSA} (vs. QMVC, r=0.6, p=0.002 and vs. TwQ, r=0.6, p=0.01).

There was no correlation between RF_{PA} and either RF_{CSA} or RF_{PCSA} measured at either 3/5 or 2/3 distances. RF_{CSA} at 3/5 distance correlated strongly with RF_{CSA} measured at 2/3 distance (r=0.9, p<0.0001) and a similar relationship was evident for values of RF_{PCSA} at the two measuring points (r=0.9, p<0.0001).

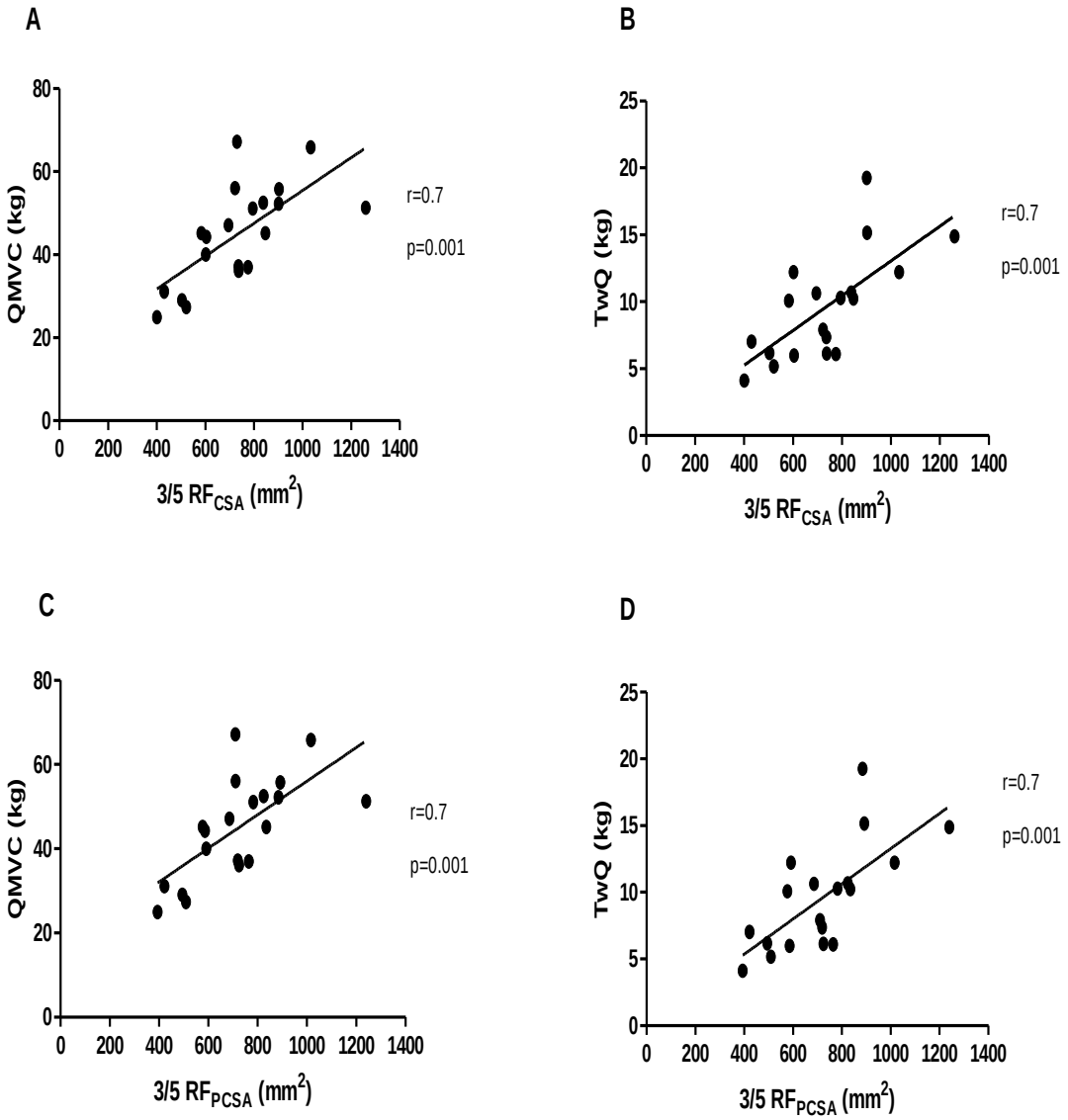


Figure 4-1 Measures of quadriceps muscle force and architecture at 3/5 distance

A. RF_{CSA} and QMVC. **B.** RF_{CSA} and TWQ. **C**. RF_{PCSA} and QMVC. **D**. RF_{PCSA} and TwQ.
p and r values derived from Pearson's correlation

Abbreviations: QMVC = quadriceps maximum voluntary contraction. TwQ = quadriceps twitch force. RF_{CSA} = rectus femoris cross-sectional area. RF_{PCSA} = rectus femoris physiological cross sectional area. 3/5 = three-fifths distance from anterior superior iliac spine to superior patellar border

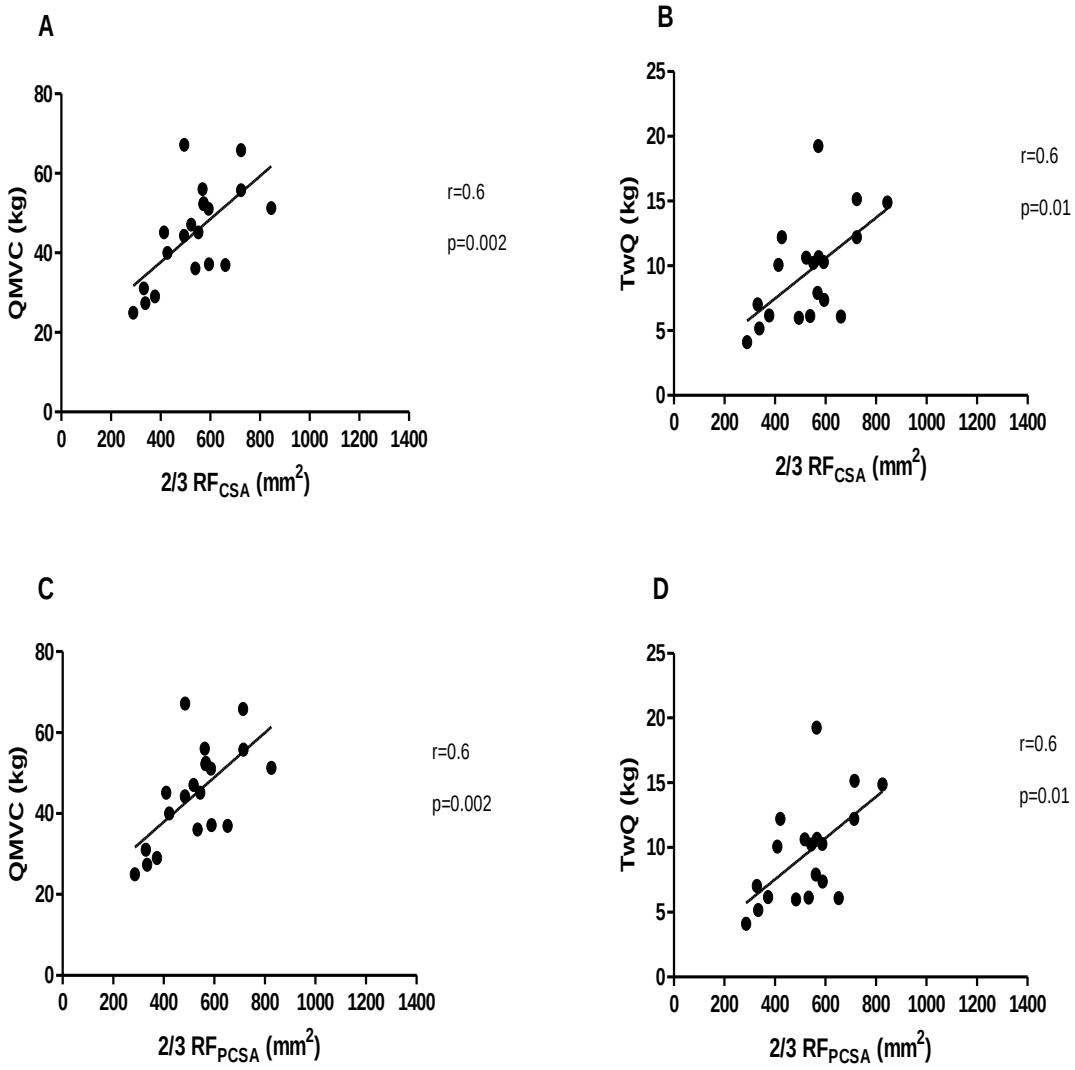


Figure 4-2 Measures of quadriceps muscle force and architecture at 2/3 distance

A. RF_{CSA} and QMVC. **B.** RF_{CSA} and TWQ. **C**. RF_{PCSA} and QMVC. **D**. RF_{PCSA} and TwQ.
p and r values derived from Pearson's correlation

Abbreviations: QMVC = quadriceps maximum voluntary contraction. TwQ = quadriceps twitch force. RF_{CSA} = rectus femoris cross-sectional area. RF_{PCSA} = rectus femoris physiological cross sectional area. 2/3 = two-thirds distance from anterior superior iliac spine to superior patellar border

4.3.2 Study 2 – Intra- and inter-observer agreement of RF_{CSA} measurements

4.3.2.1 Intra-observer agreement

Five healthy subjects (M:F 2:3), with a median (IQR) age of 26.0 (21.0-30.5)years, height of 1.64 (1.62-1.74)m and weight 63.2 (57.4-76.0)kg, underwent three measurements of RF_{CSA} at both 3/5 and 2/3 measurement points, separated by a minimum of 60 minutes. Results are shown in Table 4-3 and Table 4-4. Average co-efficients of variation were 0.4% and 0.9% for measurements performed at 3/5 and 2/3 measurement points respectively. Intra-class correlation coefficients (ICC) of 1.0 (95%CI 0.98-1.0) and 0.92 (95%CI 0.61-0.99) were found for measurements at 3/5 and 2/3 distances respectively, showing high levels of agreement.

Table 4-3 Intra-observer variability of RF_{CSA} measurements at 3/5 distance

Subject	Measurement point	Occasion			mean	SD	CV (%)
		1	2	3			
1	3/5	901.0	903.0	899.3	901.1	1.5	0.2
2	3/5	737.0	747.7	742.7	742.5	4.4	0.6
3	3/5	722.0	735.0	722.7	726.6	6.0	0.8
4	3/5	736.3	742.7	746.0	741.7	4.0	0.5
5	3/5	695.0	697.3	695.7	696.0	1.0	0.1
Mean					761.6	3.4	0.4

All ultrasound measurements in mm^2.

Abbreviations: 3/5 – three-fifths distance from anterior superior iliac spine to superior patellar border measurement point. SD = standard deviation. CV = coefficient of variation

Table 4-4 Intra-observer variability of RF_{CSA} measurements at 2/3 distance

Subject	Measurement point	Occasion			Mean	SD	CV (%)
		1	2	3			
1	2/3	571.3	560.0	573.3	568.2	5.9	1.0
2	2/3	539.0	542.0	531.0	537.3	4.6	0.9
3	2/3	568.0	563.0	560.7	563.9	3.1	0.5
4	2/3	594.3	574.0	581.5	583.3	8.4	1.4
5	2/3	523.3	517.0	520.3	520.2	2.6	0.5
Mean					554.6	4.9	0.9

All ultrasound measurements in mm^2.

Abbreviations: 2/3 – two-thirds distance from anterior superior iliac spine to superior patellar border measurement point. SD = standard deviation. CV = coefficient of variation

4.3.2.2 Inter-observer agreement

Twenty patients (M:F=14:6) with a mean (SD) age of 57.3±20.3years underwent measurement of RF_{CSA} by two clinicians (BC, Clinician 1, and a second colleague, Clinician 2). Table 4-5 summarises demographic and measurement data for the cohort. RF_{CSA} was measured at both 3/5 (n=6) and 2/3 (n=18) distances. Four patients had measurements performed at both points.

Bland-Altman analysis (Figure 4-3) demonstrates mean differences between the two clinicians for RF_{CSA} measurements (95% limits of agreement -74.4 to 64.9mm^2, mean (SD) bias -4.8(35.5)mm^2), with the majority showing very close agreement. An ICC of 0.99 (95% CI, 0.97 – 0.99) was observed indicating excellent agreement.

Table 4-5 Demographic and measurement data for critically ill cohort

Patient	Age	Gender	Distance point	Clinician 1 RF_{CSA} (mm^2)	Clinician 2 RF_{CSA} (mm^2)
1	64	M	2-3	346.3	356.0
2	82	M	2-3	206.3	214.0
3	86	M	2-3	482.0	490.7
4	63	F	2-3	292.3	368.7
5	64	M	3-5	421.0	450.7
6	82	M	3-5	303.3	315.3
7	63	F	3-5	505.3	504.7
7	63	F	2-3	260.0	260.3
8	46	M	2-3	992.0	948.3
9	59	F	2-3	228.0	206.7
9	59	F	3-5	293.7	291.0
10	27	M	2-3	828.7	865.7
11	53	M	2-3	533.7	619.7
12	45	F	2-3	360.7	257.7
13	79	M	2-3	609.0	625.0
14	18	M	2-3	498.0	481.0
15	60	M	2-3	818.7	811.7
16	28	F	2-3	371.7	383.7
16	28	F	3-5	461.7	472.7
17	65	M	2-3	454.3	458.3
18	31	F	2-3	453.0	445.7
18	31	F	3-5	573.3	583.0
19	48	M	2-3	750.0	717.7
20	83	M	2-3	273.3	261.0

When the cohort of measurements was categorised and agreement investigated according to measurement point, high levels of agreement were evident for both 3/5 (ICC 0.99 (95%CI 0.92-1.0), Bland-Altman 95% limits of agreement -82.8-81.3mm^2 (Bias -0.8mm^2) and 2/3 distances (ICC 0.98 (95%CI 0.96-0.99), Bland-Altman 95% limits of agreement -32.5-12.8mm^2 (Bias -0.8mm^2).

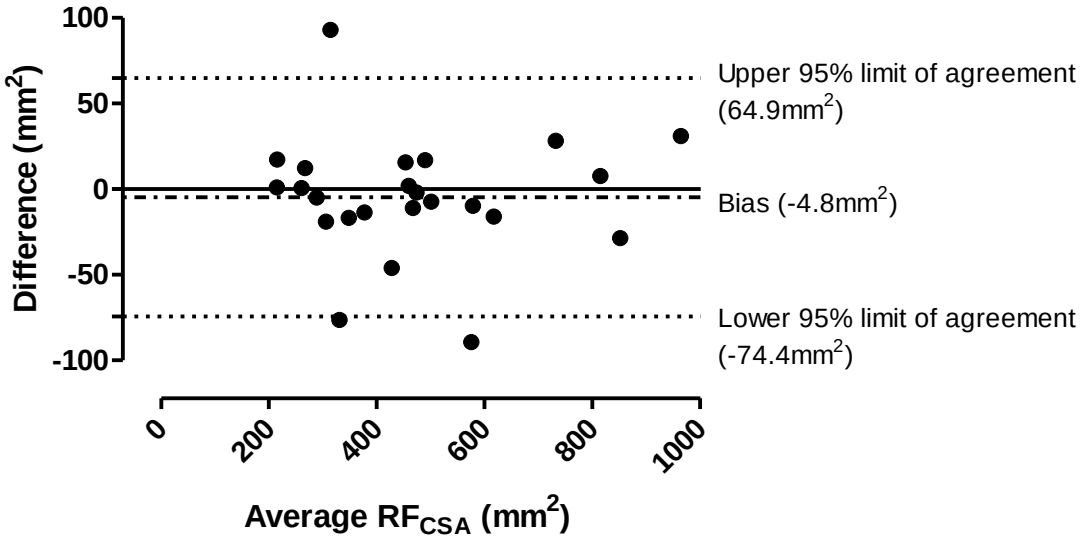


Figure 4-3 Bland-Altman plot of inter-observer agreement of average RF_{CSA} measurements

Abbreviations: RF_{CSA} = rectus femoris anatomical cross-sectional area.

4.4 Discussion

Data from the current study demonstrated that in a cohort of young healthy individuals, quadriceps rectus femoris physiological cross-sectional area (RF_{PCSA}) showed no stronger relationship with volitional and non-volitional measures of quadriceps force than the simpler measurement of quadriceps rectus femoris anatomical cross-sectional area. Interestingly, these data also showed that quadriceps rectus femoris pennation angle was independent of anthropometric factors. A relationship between RF_{CSA} measured at 2/3 distance and volitional and non-volitional measures of quadriceps strength was demonstrated, confirming and complementing the published data of the measurement at the 3/5 distance. This finding is of technical and clinical importance with regard use of ultrasound to measure RF_{CSA} in critically ill patients as these data support the reliable use the measurement of RF_{CSA} at both distances. In addition, high levels of intra- and inter-observer agreement were demonstrated for RF_{CSA} measurement, which further strongly support the use of this technique in clinical practice.

4.4.1 Critique of method

4.4.1.1 Participants

Participants in Study 1 were healthy individuals with no musculoskeletal pathology that would influence ability to perform maximum quadriceps contraction manoeuvres or preclude magnetic stimulation, or suggest changes in muscle appearance due to pathology. Furthermore, the median age of the group was 31years. Despite a maximum age of 71years, this still represents a relatively young cohort and as such limits the ability to generalise the results to a wider age range or disease group. However, this does not detract from the importance of the study that demonstrated the limited clinical utility of incorporating the more complex measurement of pennation angle and physiological cross-sectional area compared with the simple measurement of anatomical cross-sectional area.

To minimise testing burden in acutely unwell critically ill patients, a cohort of those healthy individuals participating in Study 1 completed the intra-observer agreement protocol and only inter-observer agreement was investigated in the patient group. This process is mirrored by a recent study also examining reliability of measuring muscle wasting in ICU patients using ultrasound [255], whereas in a separate study involving patients with coronary artery disease, patients were used to test both intra- and inter-observer agreement, albeit these were a stable outpatient cohort [256]. Whilst limited demographic data are reported for this patient cohort, such as preceding ICU length of stay or duration of mechanical ventilation, they represent a sample taken from a larger cohort in whom the trajectory of muscle wasting was sequentially measured using ultrasound (loss from Day 1 of admission to Day 10, 17.7% [95% CI, −25.9% to 8.1%]; $p<0.001$ [250]), and can be considered reflective of a general ICU patient cohort.

4.4.1.2 Technical considerations

In critically ill patients peripheral skeletal muscle wasting, superimposed with fluid retention, can limit the value of alternative techniques to demonstrate muscle loss such as anthropometric measures of mid-thigh circumference or fat-free mass

that rely on a balanced state of hydration [86, 257]. For example, in a pilot cohort of ICU patients RF_{CSA} was shown to significantly reduce over a ten day period, whilst thigh circumference remained unchanged [73]. Ultrasonography, which is not influenced by clinical state, has therefore been suggested as a technique to quantify muscle wasting in oedematous patients with multiple organ failure [254], and a number of investigators have reported on RF_{CSA} and muscle layer thickness using ultrasound in critically ill patients in the ICU [81-83, 86, 250, 252-254]. However the caveat to these quantitative measures is the lack of qualitative data reflecting muscle composition. Echogenicity data are emerging that may give some indication of muscle quality [81] as well as quantity. In addition contemporaneous measures of muscle force and cross-sectional area obtained in critically ill patients would confirm use of ultrasound as a surrogate marker for strength. Despite this, acquiring such muscle force data in the ICU are technically challenging, particularly for the quadriceps muscle. For this reason healthy subjects were investigated in the current study, but two measurement points on the muscle were analysed in order to provide technical validation for application of ultrasound of RF_{CSA} in critically ill patients. Previous studies have employed use of CT scans to validate RF_{CSA} measurements in both healthy subjects and patients with chronic respiratory or cardiac disease [73, 256]. Whilst these data have proven the accuracy of ultrasonographic measurement in these patient groups, this method of confirmation of findings was not feasible for the ICU patient population in the current study. Furthermore reliability of measures over time was also not possible due to the potential for further muscle wasting during interim days.

Quadriceps rectus femoris pennation angle data in the current study were obtained from the average of three consecutive readings. Image acquisition occurred when individual fibres could be visualised inserting into the aponeurosis separating quadriceps rectus femoris from the vastus intermedius muscle beneath [93, 97, 99, 102]. Calculation of RF_{PA} was performed using offline imaging software. Variation in screen resolution between the ultrasound and offline 'measurement' screens could have affected image quality making discernment of the insertion point of fibres onto the aponeurosis difficult to establish resulting in potential over or underestimations of angles. However, the agreement between

online and offline measurement has been demonstrated earlier in this thesis (*Chapter Three, Methods*), although only for RF_{CSA}.

Repeatability of quadriceps rectus femoris pennation angle was not undertaken in this study which could be considered a limitation of the protocol. Future studies should examine reliability and validity of ultrasonographic assessment of all parameters of peripheral skeletal muscle architecture in critically ill patients, and this may also include echogenicity. Acquisition of these data would further substantiate use of ultrasound as a method of muscle evaluation in this patient population.

4.4.2 Clinical interpretation

A correlation between RF_{CSA} measured at 3/5 distance and both volitional and non-volitional quadriceps force was demonstrated in keeping with that found in similar studies [65, 73]. Furthermore, this relationship was also observed at 2/3 distance, strongly supporting that both measurement points may be used in clinical practice as a surrogate marker of muscle force generation. This is relevant for those critically ill patients who present without any pre-existing muscle pathology or wasting and where complete visualisation of RF_{CSA} at the more proximal measurement point is often not possible due to the size of the muscle itself. In the current study, quadriceps rectus femoris physiological cross-sectional area showed a similar relationship with volitional and non-volitional quadriceps muscle force as RF_{CSA}, and thus the principle variable contributing to physiological cross-sectional area is, in fact, anatomical cross-sectional area rather than pennation angle. In part, this is a reflection of the muscle adopting a pennate arrangement to facilitate muscle location in the body, whereas a parallel fibre arrangement is not possible, and with pennate muscles losing a proportion of strength relative to the size of the pennation angle.

Rutherford *et al* [97] found a significant correlation between pennation angle, derived from an average angle for vastus intermedius and lateralis muscle components of quadriceps, and cross-sectional area. The different anatomical position of rectus femoris could explain the findings of the current study where

there was no such relationship between rectus femoris pennation angle and cross-sectional area observed, if varying muscle position results in differing fibre pennation angles. Further exploration of the relationship between pennation angle and quadriceps strength in disease groups where muscle pathology may be evident, such as critical illness may still be warranted, in particular if the angle was shown to alter with effects of training programmes to address muscle loss. Significant reductions in pennation angle of the vastus lateralis muscle have been shown in healthy subjects following five weeks of horizontal bed rest [93], a scenario applicable to acute patients experiencing critical illness. It could be anticipated that similar findings, if not greater reductions, may be evident in this patient group especially those with chronic co-morbidity that may further exacerbate muscle pathology.

As expected, quadriceps force measures differed significantly between males and females but with similar levels of percentage muscle activation demonstrated during manoeuvres. As previously mentioned, participants were healthy subjects with no musculoskeletal pathology to influence performance of maximum volitional efforts for force generation. The range of muscle activation evident showed that some individuals were delivering their maximum effort, whilst others may have had the capacity for further force generation. This would be akin to scoring either Level 5 or Level 4 on the MRC scale [34]. If, using accurate physiological measurement under laboratory conditions, healthy individuals can demonstrate muscle strength performance that would translate to variable scoring on the MRC scale, then the potential for inaccuracy in measuring patients in acute clinical settings such as the in ICU is likely to be greater still. This has potentially significant clinical implications if, for example, observed strength is one factor used in guiding delivery of physical rehabilitation interventions. Furthermore the crude nature of ordinal MRC scale, means that variation in force between levels may not be detected. That females demonstrated reduced force compared to males has been similarly reported in patients with ICU-acquired weakness, where cut-offs for handgrip dynamometry were lower in women than in men [36]. Levels of intra- and inter-observer RF_{CSA} agreement were in keeping with previous studies [73, 255, 256] albeit the smaller sample size for intra-observer agreement in the

current study (n=5) resulted in a greater impact from individual subject variation meaning 95% confidence intervals were very wide for the 2-3 distance.

4.5 Conclusion

Surprisingly, in a cohort of young healthy individuals, quadriceps rectus femoris physiological cross-sectional area failed to demonstrate a stronger relationship with quadriceps force than quadriceps rectus femoris anatomical cross-sectional area. Pennation angle was found to be independent of anthropometric measurements and there was no correlation between pennation angle and either anatomical or physiological cross-sectional area. At present it is reasonable to use anatomical cross-sectional area to investigate the trajectory of muscle wasting during critical illness. Nonetheless, further exploration of pennation angle in disease states may still be valuable and indeed assessment of pennation angle before and after training needs investigation. A relationship between quadriceps rectus femoris anatomical cross-sectional area measured at the 3/5 distance and 2/3 distance and quadriceps strength was confirmed supporting the use of either measurement point in clinical practice, depending on the premorbid clinical state of the patient. The high levels of intra- and inter-observer agreement for quadriceps rectus femoris anatomical cross-sectional area also strongly support the clinical reliability of ultrasound cross-sectional area measurement as a tool for assessing muscle wasting in critically ill patients.

Chapter 5 Ultrasound for the Assessment of Peripheral Skeletal Muscle Architecture in Critical Illness: a Systematic Review

5.1 Introduction

Peripheral skeletal muscle wasting and weakness are major complications of critical illness. Loss of muscle strength is commonly referred to as intensive care unit acquired weakness (ICU-AW) [5] and observational studies report a high prevalence of ICU-AW affecting up to two-thirds of all critically ill patients [37]. As expected, ICU-AW is associated with prolonged weaning, delayed rehabilitation, increased hospital length of stay and increased mortality [11, 29, 30, 36, 37, 40-42, 258]. In survivors of critical illness, significant and prolonged physical functional impairment and disability are evident, with deficits persisting up to five years following the index ICU admission [103-105, 259].

Early identification of those patients at risk of developing peripheral skeletal muscle wasting and ICU-AW using clinically useful tools for monitoring muscle dysfunction is key to successful patient management [140]. Risk stratifying patients with peripheral skeletal muscle wasting and weakness will allow exercise therapy, rehabilitation and other therapeutic interventions to be directed to those patients who are most likely to benefit. Volitional methods of measuring muscle strength, such as manual muscle testing including the MRC-SS [35] and handgrip dynamometry [36], are often appealing due to their speed, ease of application and minimal testing equipment. However these assessments are restricted to those alert, awake and cognitively intact patients, able to produce maximal efforts during testing. Distinguishing between actual muscle weakness, poor motivation and inability to complete the task is challenging, and hence their use in patients in the early stages of critical illness is limited [57, 60].

Although non-volitional techniques involving electrical [65, 66] and magnetic [63, 64, 260, 261] nerve stimulation of peripheral motor nerves to elicit a twitch force response of a muscle require limited patient cooperation, these techniques are technically complex to perform, in particular, within the ICU environment. Furthermore these tests require expensive, dedicated equipment and skilled personnel for both assessment and interpretation [19].

Given the caveats associated with both volitional and non-volitional strength measurement in critically ill patients, recent attention has focused on the utility of ultrasound to monitor the trajectory of muscle wasting in critically ill patients [262]. Ultrasonographic differences have been demonstrated between healthy and diseased muscle [263, 264] and studies in healthy subjects and patients with chronic respiratory disease have demonstrated that peripheral skeletal muscle cross-sectional area, measured using ultrasound, correlate closely with muscle strength [73, 102, 265]. Ultrasound therefore acts as a surrogate where direct strength measurement is not feasible. The technique of peripheral skeletal muscle ultrasound has been reported in previous reviews [87-89, 91] and a number of characteristics of peripheral skeletal muscle, including cross-sectional area, fibre pennation angle, muscle layer thickness and echogenicity [98] have been described. The use of ultrasound also has both pragmatic and clinical advantages, which have been discussed in earlier chapters of this thesis.

5.1.1 Aim of study

The objective of this study was to conduct a systematic review to critically evaluate and synthesise evidence for the use of ultrasound to measure peripheral skeletal muscle architecture during critical illness. This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [266].

5.2 Methods

5.2.1 Protocol registration

The protocol for this systematic review was registered on the National Institute for Health Research (NIHR) International Prospective Register of Systematic Reviews (PROSPERO) (Registration reference CRD42013004892, available at http://www.crd.york.ac.uk/prospero/).

5.2.2 Eligibility criteria

Study characteristics for eligibility are detailed in Table 5-1, including details of participants, interventions, control groups and outcome measures.

Table 5-1 Eligibility criteria for studies

Characteristic	Inclusion	Exclusion
Study Design	Quantitative study design including randomised controlled trials, pseudo-randomised controlled trials, cohort, cross-sectional, case series, case control studies or case studies [267, 268]	Studies not reported in a peer-reviewed journal, descriptive commentary, conference abstracts or proceedings, preliminary reports when results are published in full in a later version
Participants	Adult patients (aged ≥18years) admitted to the intensive care unit with critical illness (irrespective of causal diagnosis)	Animal studies; studies conducted solely in high dependency, long-term weaning or acute ward settings
Intervention	Ultrasound for measurement of any characteristic of peripheral skeletal muscle architecture	Non-peripheral skeletal muscle.
Control/Comparator	Not applicable. No control or comparators.	
Outcome measures	Measures of any characteristic of peripheral skeletal muscle architecture	
Publication	No publication date or language restriction will be applied during the initial search	Non-English language studies will be excluded from further review after the initial search

5.2.3 Information sources

Prior to conducting this review, the Cochrane Library, Physiotherapy Evidence Database (PEDro) and the NIHR PROSPERO database were searched to confirm a review of this nature had not been published or was in progress, and this was confirmed.

Electronic databases (n=7) were searched by one reviewer (the researcher, BC) using a systematic comprehensive and reproducible search strategy to identify published evidence studies (Table 5-2). Databases were accessed via the author's institution, King's College London, and included Medline (1946-present), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981-present), Cochrane Library (2013), PEDro (1993-present), Scopus (1960-present),

Excerpta Medica Database (EMBASE) (1980-present) and Web of Science (including Science Citations and Conference Proceedings) (1900-present), with the last search run 16th October 2013. Details of full search strategies are included in *Appendix IV*. Additional references were identified by cross-checking reference lists of included articles and searching the personal library of the author.

Table 5-2 Search strategy

Name of database	Search fields	Search terms (MESH Indexing and free text)
Medline, Cochrane Library, CINAHL, EMBASE, PEDro, Web of Science, Scopus	Title, abstract, key words	i) intensive care; critical care; critical illness; critically ill; multi organ failure; sepsis; ii)ultrasound; ultrasonography; iii) muscle; muscle wasting; muscle mass; cross-sectional area; fibre (or fiber) pennation angle; muscle layer thickness; echo intensity; echogenicity; muscle architecture iv) #1 and #2 and #3

Abbreviations: CINAHL = Cumulative Index of Nursing and Allied Health Literature. EMBASE = Excerpta Medica Database. PEDro = Physiotherapy Evidence Database.

5.2.4 Search

Trial registries, conference proceedings and electronic databases were searched using the following terms as MESH Indexing subject headings and free text search terms: intensive care, critical care, critical illness, critically ill, multi-organ failure, sepsis, ultrasound, ultrasonography, muscle, muscle wasting, muscle mass, cross-sectional area, fibre pennation angle, muscle layer thickness, echo intensity, echogenicity, muscle architecture (Table 5-2).

5.2.5 Study selection

Figure 5-1 summarizes the study selection process. Two independent reviewers (BC and a second reviewer) assessed studies for eligibility following a standardized process. The title and abstract of all articles identified through the initial search process were used to determine eligibility against the predefined eligibility criteria (Table 5-1). If there was insufficient information to inform a

decision, full text was sourced and independently reviewed again (BC and a second reviewer). At both stages, in the event of disagreement a consensus approach was taken. If agreement could not be reached, a third reviewer was employed to make the final decision. At each eligibility assessment stage, level of agreement was determined using percentage agreement and Kappa statistic (SPSS for Windows, Statistical Version 20, IBM, New York, NY). All references were stored in Endnote software, Version 6 (Thomson Reuters, Philadelphia, PA).

5.2.6 Data extraction

A bespoke data collection form was designed, and data extraction from included studies performed by one reviewer (BC) and cross-checked by a second reviewer. Data were stored in either Microsoft Excel or Word for PC 2007 (Windows 7, Microsoft Corporation, Redmond, WA).

5.2.7 Data items

Data extraction was conducted on all eligible studies including: (1) study design – type, author first name and country, publication journal and year, aim/objective; (2) participant characteristics; (3) ultrasound detail – timing of measurement, muscle groups and muscle architecture characteristics assessed, detail of technique, and results.

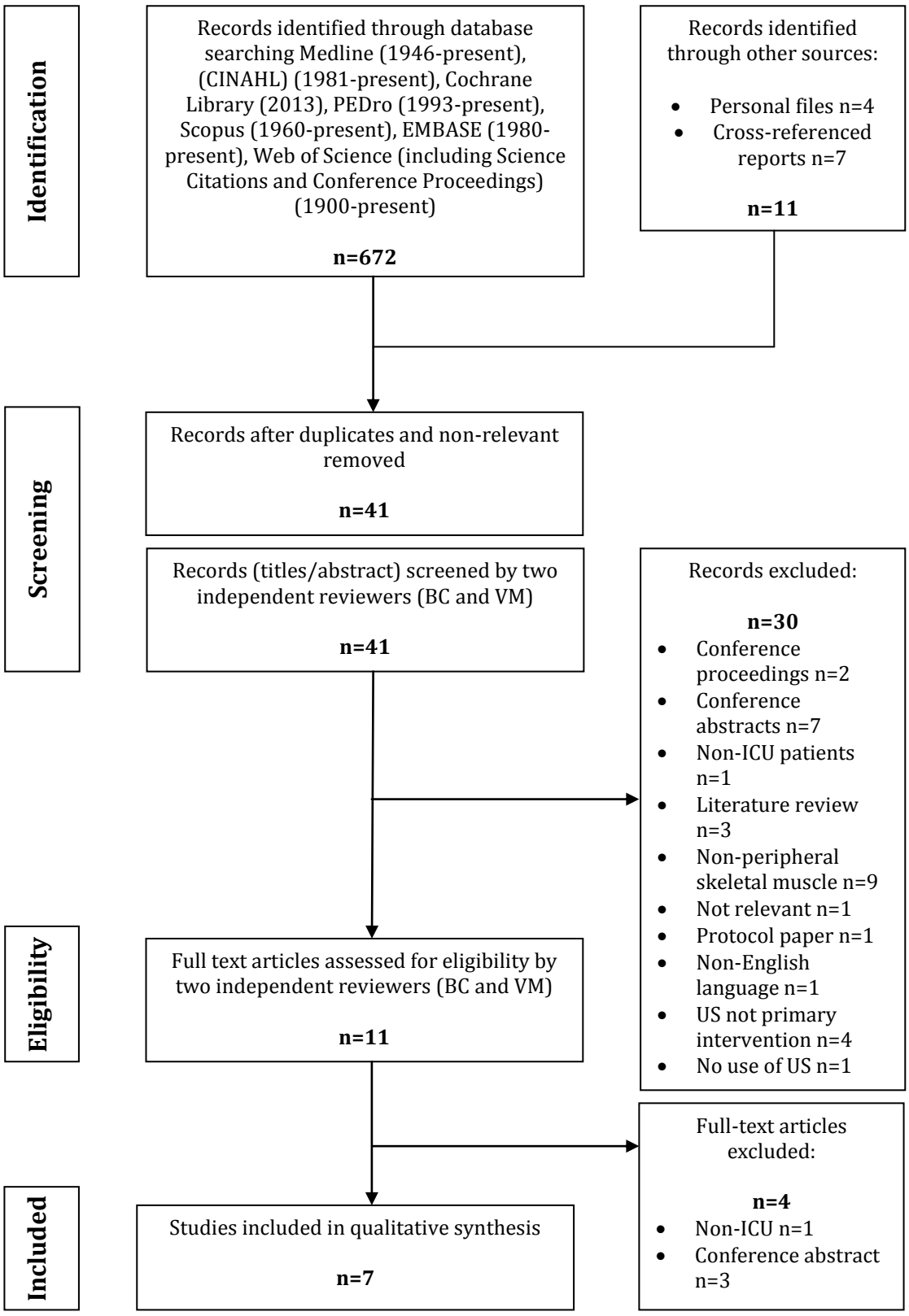


Figure 5-1 Flow diagram summarising article selection

Abbreviations: CINAHL = Cumulative Index to Nursing and Allied Health Literature. EMBASE = Excerpta Medica Database. PEDro = Physiotherapy Evidence Database. ICU = intensive care unit. US = ultrasound. BC = initials of the researcher. VM = initials of the second reviewer.

5.2.8 Risk of bias in individual studies

Two independent reviewers (BC and a second reviewer) assessed the included studies. Study design was determined using a published classification algorithm from the Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute for Health and Care Excellence, with associated relevant checklists employed to assess study quality [267, 269]. Studies were graded according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence [268]. In addition methodological quality and risk of bias in randomised controlled trials (RCTs) were determined using the PEDro scale [270], and the Newcastle-Ottowa Scale (NOS) [271] for nonrandomised observational studies.

5.3 Results

5.3.1 Study selection

Searching of the seven databases resulted in 672 potentially eligible studies, with a further 11 articles identified through cross-referencing and personal libraries (Figure 5-1). Studies not published in English were excluded (n=1). Two conference proceedings were checked but there were no relevant studies identified. For the remaining conference abstracts (n=10), two studies within the author's own library contained data pertaining to four of these abstracts. The authors of a further two abstracts were contacted to determine if data were available in peer-reviewed publication format, following which neither study was included. No contact was made with the remaining four abstract authors as data had been collected in non-ICU settings (n=2), in healthy subjects (n=1) or no email address or other contact details were available (n=1).

High levels of agreement between the two independent reviewers were evident for potentially relevant titles/abstracts (BC and a second reviewer) (percentage agreement=90.2%, Kappa=0.72) and full-text articles (BC and a second reviewer) (percentage agreement=100.0%, Kappa 1.0). The reviewers disagreed on four potentially eligible studies based on title and abstract. Following consensus, agreement was reached on all four studies and none of these studies were

included. Input from a third reviewer was therefore not required. Review of title, abstract and full text resulted in the inclusion of seven original articles each evaluating unique patient cohorts.

5.3.2 Study characteristics

Study design characteristics are summarized in Table 5-3. None of the seven included studies [81, 82, 86, 250, 252-254] were randomised controlled trials. Six were primarily single group studies, classified as case series [81, 82, 86, 250, 253, 254]. One of these studies involved comparison with an unmatched control group [253]. The final study adopted a case-control design [252]. All studies were Level 4 evidence grade [268]. Significantly, the majority of included studies were published between 2012 and 2013 [81, 250, 252, 253] indicating the recent increasing research interest in ultrasound as a technique for evaluating changes in peripheral skeletal muscle architecture during critical illness. Five studies were based in Europe [82, 83, 250, 253, 254], with one conducted in Australia [252] and one in North America [81]. Patient characteristics of included studies are reported in Table 5-4.

Of the seven studies included, each involved independent general ICU patient populations, totaling 300 patients overall where the primary purpose involved assessment of peripheral skeletal muscle function during critical illness with ultrasound as the evaluation tool. Sample sizes ranged between 9 [254] and 118 [82] patients (Table 5-4). Eligible patient populations in studies were characterized according to either clinical diagnostic descriptors (e.g. multi-organ failure and sepsis) [81, 253, 254], ICU admission-related descriptors (e.g. duration of mechanical ventilation and length of stay) [82, 250], or a combination of both [86, 252]. Only four studies reported actual illness severity of their patient cohorts using standard critical care scoring systems (APACHE scores) [86, 250, 252, 253], of which three further reported actual duration of mechanical ventilation for their patient cohorts [250, 252, 253].

Table 5-3 Outline of aims and design of included studies

Reference	Study Aim(s)	Detail of Study Design	Study Classification and Evidence Level
Campbell *et al* [254]	Establish a relation in normal individuals between fat-free mass derived from body weight and skinfold thickness measurements and muscle thickness measured by ultrasound, and compare lean tissue mass in subjects with and without oedema	Prospective double group; separate cohorts of patients and healthy subjects; groups investigated individually and not compared	Non-comparative case series Level 4
Gruther *et al* [82]	Determine if ultrasound measurements are valid and practical for assessing muscle mass in daily routine in ICU patients; measure muscle wasting in ICU patients over a 28day period and determine the relationship with LOS	Prospective "two-fold"; two patient cohorts; groups investigated individually and not compared	Non-comparative case series Level 4
Reid *et al* [86]	Determine if ultrasound measurement of muscle wasting is applicable to a larger and sicker ICU population than previously reported ([254]); determine the relationship between muscle wasting and energy balance	Prospective single patient cohort	Non-comparative case series Level 4
Baldwin *et al* [252]	Determine muscle strength and size in respiratory and limb muscles of critically ill survivors of sepsis compared to healthy controls; determine relative effects in the degree of dysfunction between muscle groups	Prospective cross-sectional design with case-controlled element; patient cohort and healthy matched control subjects	Case control study Level 4
Cartwright *et al* [81]	Track changes during ICU admission of muscle layer thickness and echotexture in distal and proximal muscles, including the diaphragm	Prospective single patient cohort	Non-comparative case series Level 4
Grimm *et al* [253]	Evaluate if muscle ultrasound allows visualisation of changes in the muscle architecture during the early course of sepsis	Prospective double group; patient cohort and unmatched healthy control subjects; groups compared	Non-comparative case series Level 4
Puthucheary *et al* [250]	Characterise and evaluate the time course and pathophysiology of acute muscle loss in critical illness and the role of alterations in protein synthesis and breakdown in such changes	Prospective single patient cohort	Non-comparative case series Level 4

Study classification determined according to algorithms from Scottish Intercollegiate Guidelines Network and National Institute for Health and Care Excellence [267, 269]. Evidence level according to the Oxford Centre for Evidence Based Medicine [268]

Abbreviations: ICU = intensive care unit. LOS = length of stay.

Muscle thickness was the most common characteristic of muscle architecture evaluated (five studies) (Table 5-5) [81, 82, 86, 252, 254]. In one study, this was termed muscle layer thickness and used to reflect muscle mass [82]. Muscle composition using echogenicity was investigated in two studies [81, 253], and cross-sectional area in one [250]. A combination of mid-upper arm, forearm and thigh muscle groups were all measured in four studies [86, 252-254]. In addition, tibialis anterior and abductor digiti minimi muscle were also reported [81, 253]. The quadriceps muscle alone was measured in two studies [82, 250]. Details of measurement procedure were provided in all studies (Table 5-5). Timings of measurements varied between single measurements performed at specific time-points during ICU admission [81, 82, 250, 252, 253], or sequentially throughout the duration of ICU admission [86, 254].

5.3.3 Results of individual studies

Results of individual studies are reported in Table 5-6. Change in muscle architecture of critically ill patients was evident in six studies and associated with duration of time in the ICU [81, 82, 86, 250, 253, 254]. In the remaining case-controlled study, muscle thickness was found to be significantly reduced compared to case-controlled healthy subjects at the single time-point assessed [252]. Rates of reported muscle wasting varied between 6.0% per day [254] and 1.6% per day, with more notable wasting in patients with greater muscle layer thickness at baseline [86]. A third study reported a 12.5% reduction between days 1 and 7, which further differed significantly between those with single-organ failure and multi-organ failure [250]. A quantifiable measurement of the degree of muscle wasting was not given in one study [82]. Muscle quality (echogenicity) was shown to be affected during critical illness with increases in image grey-scale values [81, 253] which were significantly different to healthy controls, albeit an unmatched population [253]. Three studies reported high levels of ultrasound image reproducibility in critically ill patients (intraclass correlation coefficients (ICC) >0.9), for inter-image (muscle thickness and muscle echogenicity) [252, 253], intra-rater (muscle echogenicity) [253] and inter-observer (muscle cross-sectional area) [250] agreement. Reid *et al* [86] also presented reproducibility data, reporting a coefficient of variation (CV) for total muscle thickness of 2.5% although

this was in a separate cohort of healthy volunteers rather than their ICU patient cohort. Similarly, Campbell *et al* [254] reported an intra-observer CV of 1.5% and an inter-observer CV of 1.9% for total muscle thickness in a cohort of healthy subjects assessed within their study.

5.3.4 Risk of bias within studies

Two independent reviewers (BC and a second reviewer) agreed on the study design of included studies (percentage agreement=100%). Due to the nature of study design assigned to the majority of studies (n=6, case series) involving single groups of patients receiving ultrasound measurements of peripheral skeletal muscle architecture during critical illness using ultrasound, there was no tool available to assess risk of bias in these studies [269]. The reviewers considered that the design of one of these studies [253], involving a comparison with an unmatched control group, did not meet the criteria for categorisation as a case-controlled study with associated quality review. The single identified case-controlled study (Baldwin *et al* [252]) demonstrated positive scoring on seven out of eleven binary outcome criteria according to the SIGN checklist (63.6%), and percentage agreement of 84.6%, however no grading system exists to equate this to an overall descriptor of quality level [269]. This article scored 6 on the NOS indicating 'good' overall quality [271].

5.3.5 Synthesis of results

Meta-analysis or pooling of results was not appropriate due to the observational nature and design of studies included, heterogeneity of patient cohorts, and varying results related to different aspects of peripheral skeletal muscle architecture measured.

Table 5-4 Patient characteristics in included studies

Author, location	Population	n	Age (years)	Gender M:F	Illness Severity	Duration MV (days)
Campbell *et al*, UK [254]	MOF requiring artificial support of ≥2 organs	9	63 (58-68)	8:1	No specific marker reported; patients were (1) fed via IV, enteral, or both; (2) mechanically ventilated; (3) invasively haemodynamically monitored with inotropic support	Not specified
Gruther *et al*, Austria [82]	Group A, ICU LOS >28days Group B, ICU LOS >7days	Group A, n=17 Group B, n=101	Group A, 55±17 Group B, 55±15	Group A, 14:3 Group B, 74:27	No specific marker reported; Patients received standard drug treatment	Not specified
Reid *et al*, UK [86]	Sepsis or SIRS, mechanical ventilation >5 days	50	57 (19-79)	26:24	APACHE II 17 (2-43)	Not specified
Baldwin *et al*, Australia [252]	Septic, requiring mechanical ventilation ≥5d	16	62±17	9:7	APACHE III 94±36	13 (7-27)
Cartwright *et al*, US [81]	Acute respiratory failure	16	59.3	7:9	No specific measure reported	Not specified
Grimm *et al*, Germany [253]	Severe sepsis or septic shock	28	69.5 (61.5-75.3)	25:3	APACHE II 22.5±6.5	20.5±13.7
Puthucheary *et al*, UK [250]	Intubated >48hrs, critical care LOS >7days, predicted ICU survival	63	54.5 (50.0-59.1)*	37:26	APACHE II 23.5 (21.9-25.2)*	10 (6-22)

Data presented as mean±standard deviation, median (Interquartile range), or mean (95% confidence intervals)*

Abbreviations: MV = mechanical ventilation. M = males. F = females. MOF = multi-organ failure. SIRS = systemic inflammatory response syndrome. IV = intravenous. ICU = intensive care unit. LOS = length of stay. APACHE II/III = Acute Physiology and Chronic Health Evaluation (version II or III)

Table 5-5 Detail of peripheral skeletal muscle architecture measured using ultrasound in included studies

Reference	Technical Detail	Muscle Architecture Parameter/ Muscle group(s)/ Procedure
Campbell et al [254]*	ALOKA SSD 500 portable US machine, equipped with 3.5MHz linear array transducer Measurements made using built-in electronic calipers on frozen, real-time cross-sectional images Mean of three measurements at each site used for statistical analysis	Muscle thickness Biceps (biceps brachia and coracobrachialis); Forearm; Thigh (quadriceps muscle group) *Mid-Upper arm anteriorly* Patient supine, elbow flexed to 90°, point marked on the skin midway between the tip of acromion and tip of the olecranon. Subject supine, elbow extended, forearm supinated, thickness of the flexor compartment measured over biceps between the superficial fat-muscle interface and the humerus *Forearm* Patient supine, elbow extended, forearm supinated, point marked midway between antecubital skin crease and the ulnar styloid. Flexor compartment thickness measured anteriorly between superficial fat-muscle interface and the interosseus membrane *Thigh* Patient supine, knee extended, midway point marked between tip of the greater trochanter and lateral joint line of knee. Thickness of the quadriceps muscle group between the superficial fat-muscle interface and the femur measured anteriorly
Gruther et al [82]	HDI-100 ATL portable US machine with an L7-4 transducer with a 5cm linear array footprint Mean MLT calculated as mean of measurement i) and ii)) on each leg	Muscle mass (muscle layer thickness) Quadriceps vastus intermedius and rectus femoris Vastus intermedius and rectus femoris assessed bilaterally at i) border between lower and upper two-thirds, and ii) mid-point between ASIS and upper pole of patella, patient supine, legs relaxed lying flat in extension

Reid et al [86]	ALOKA Echo Camera SSD-210DXII portable ultrasound machine with a 5MHz linear array transducer	Muscle thickness Mid-upper arm (biceps and brachialis); Forearm; Thigh
	Measurements made using built-in electronic calipers on frozen, real-time cross-sectional images	*Mid-Upper arm* Patient positioned in supine. Measured over the biceps down to the humerus, at a point midway between the tip of the acromion and the tip of the olecranon, with elbow extended and forearm supinated
	Mean of three measurements used for statistical analysis	*Forearm* Patient positioned in supine. Measured down to the interosseus membrane at a point midway between the antecubital skin crease and ulnar styloid, with elbow extended and forearm supinated
	Mean values from three sites combined to indicate total lean body mass	*Thigh* Patient positioned in supine. Measured down to the femur, on the anterior surface of the thigh, midway between the tip of the greater trochanter and the lateral joint line of the knee identified
Baldwin et al [252]*	DP-6600 Shenzhen Mindray Bio-medical Electronics portable US machine with a 10MHz 38mm linear transducer array	Muscle thickness Mid-upper arm; Mid-forearm; Mid-thigh
	Three measurements taken per muscle group	*Mid-upper arm* Measured to the humerus, with patient supine, elbow extended and arm neutrally rotated in slight abduction (≈10°) alongside the body
	Transducer placed at the most anterior facing aspect of each segment, in the transverse plane from the mid-segment point	*Mid-forearm* Measured to either mid-way point between radius and ulna along the interosseus membrane, or, where interfaces most parallel, depending on individual patient anatomy; forearm positioned with sufficient supination to improve visualization of interosseus membrane. Patient positioned in supine
	Technique in keeping with that previously reported by Baldwin *et al* [272]	*Mid-thigh* Measured to femur, with the knee extended and leg in neutral abduction and rotation. Patient positioned in supine

Cartwright et al [81]*	Esaote Biosound MyLab 25 portable ultrasound machine with an 18-MHz linear-array transducer Settings - overall gain 76%, time-gain compensation in the neutral position, single focal zone, power of 75%, mechanical index 0.5, constant depth settings (except where large volume of subcutaneous edema require alterative settings to view muscle) For grey-scale data, 2cmx2cm region of interest was placed over the representative muscle (1cmx1cm for abductor digiti minimi)	Muscle thickness, subcutaneous tissue thickness, mean (standard deviation) of grey-scale values Tibialis anterior; Rectus femoris; Abductor digiti minimi; Biceps brachii and brachialis complex Measurements taken at 5cm distal to fibular head (tibialis anterior), 15cm proximal to the superior portion of the patella (rectus femoris), middle of the fifth metacarpal (abductor digiti minimi), 10cm proximal to the antecubital fossa (biceps brachii and brachialis complex). Patient position not specified
Grimm et al [253]	Siemens Acuson portable US machine with a 9-13MHz linear transducer array scanner Settings – kept constant during all examinations excluding depth, which was altered individually to visualize complete muscle Echogenicity graded using the Heckmatt scale – 4-point scale where higher grades of echotexture correlates to severity	Muscle echogenicity Biceps brachii; Quadriceps femoris; Forearm extensors; Tibialis anterior Patients supine with arms and legs in relaxed extension; measurements taken at the midline between origin and insertion (biceps brachii and quadriceps femoris), the first third distance between elbow and processus styloideus radii (forearm extensors) and first third between knee and malleolus lateralis (tibialis anterior)

	of muscle impairment; echotexture scores for four muscle regions averaged to generate a mean echotexture score	
Puthucheary et al [250]	PLM805 Toshiba Medical Systems portable US machine, B-mode with an 8MHz 5.6cm linear transducer array; Philips Envisor HD 1.3 portable US machine, B-mode with a 6-15MHz 4cm linear transducer array Overall cross-sectional area taken as the average of three consecutive measurements within 10%	Cross-sectional area Quadriceps rectus femoris Transducer placed perpendicularly along the superior aspect of the thigh, two-thirds distance between anterior superior iliac crest and the superior patellar border; patients in supine with 30° head elevation unless clinically unfeasible

*only detail provided regarding peripheral skeletal muscle data in critically ill patients. Campbell *et al* [254] additionally measured calf, trunk and triceps muscle groups in healthy subjects, Baldwin *et al* [252] additionally measured the diaphragm in the critically ill cohort, and all muscle groups in healthy controls, Cartwright *et al* [81] additionally measured the diaphragm.

Abbreviations: MOF = multi-organ failure. US = ultrasound. ICU = intensive care unit. LOS = length of stay. MLT = muscle layer thickness. ASIS = anterior superior iliac spine.

Table 5-6 Data demonstrating changes in muscle architecture measured using ultrasound from included studies

Reference	Timing of Measurement	Results
Campbell et al [254]*	Commenced within 5days of MOF onset and ICU admission	Median (max-min) rate of muscle wasting (expressed as percentage of first measurement), 6.0 (2.0-9.2)% per day
	Serial measurements performed every 1-4days for between 5 and 11 days, with a minimum of 5 measurements per patient	Significant negative correlation between muscle thickness and time (max-min r=-0.919 to -0.978, p=0.027 to <0.001)
Gruther et al [82]	Group A: measurements performed twice, once at baseline (random LOS, at least 1 day after ICU admission) and after 28d of ICU admission	*Group A* MLT measurements in both legs showed a reduction (n=27 thighs) and an increase (n=7 thighs) between time-points; high significant negative correlation between MLT of the right (p=0.005) and left (p=0.004) thigh, and MLTD (MLT difference at 28days) for the right (p=0.006) and left (p=0.003) thigh, and LOS at ICU baseline measurement time; LOS at ICU baseline measurement time the only variable influencing MLTD on the right (p=0.006) and left (p=0.003) thigh
	Group B: one measurement performed after a random ICU LOS	*Group B* High significant negative correlation between MLT of the right (p<0.0001) and left (p<0.0001) thigh and LOS at ICU baseline measurement; LOS at ICU baseline measurement (p<0.0001) and thigh circumference (p=0.006) only variables that influenced right thigh MLT; LOS at ICU baseline measurement (p<0.0001), thigh circumference (p<0.0001) and height (p=0.016) only variables influencing left thigh MLT
Reid et al [86]	Measurements performed every 1-3days, in keeping with method described by Campbell *et al* [254], for between 7 (5-39)days	Total muscle thickness decreased with time in 96% of patients (n=48/50) (r^2=-0.953, p<0.001); median (range) rate of decrease as percentage of baseline 1.6 (0.2-5.7)%/day; 2 patients demonstrated increases of 1.1 and 0.6%/day
		Non-significant difference in percentage change in muscle thickness between those patients whose mid-upper arm circumference decreased (% change -1.3(-0.2 to -4.0)) or remained the same (% change -1.6 (-0.3 to -4.2))
		Loss of muscle thickness over the first 7 days significantly higher in patients with greater muscle thickness at

		baseline (at baseline 'thicker' muscle 5.25 (4.3 to 6.8)cm vs. 'thinner' muscle 3.75 (2.6 to 4.2)cm, p<0.001; total change in 7 days -0.8 (-0.2 to -2.3)cm vs. -0.35 (0.0 to -1.1)cm, p=0.001); when loss expressed as percentage of first measurement p=0.051
Baldwin et al [252]*	Measurements performed at median (IQR) 16 (11-29)days of ICU admission	Excellent reproducibility of triplicate measurements of peripheral skeletal muscle thickness (ICC ≥0.976) Muscle thickness significantly lower in critically ill patients compared to healthy controls - upper arm (25.1±4.3 vs. 20.6±4.4mm, mean difference 4.5mm, 95% CI 1.3-7.6mm, p<0.01), forearm (29.8±4.6 vs. 22.6±4.9mm, mean difference 7.2mm, 95%CI 3.8-10.6mm, p≤0.001), thigh (29.0±5.8 vs. 16.8±6.1mm, mean difference 12.2mm, 95%CI 7.9-16.5, p≤0.001) – when corrected for fat-free mass, only thigh muscle thickness was significantly correlated Significant difference in all peripheral skeletal muscle thicknesses compared to the diaphragm (p≤0.001)
Cartwright et al [81]*	Measurements performed at baseline (within 80hours of ICU admission), and days 3, 7, 14 after baseline (if still in hospital); 2, 4 and 6 months after hospital discharge	Significant increase in TA mean grey-scale value over 14days of ICU admission (138.39 to 166.39, p=0.027), with significant reduction in grey-scale standard deviation (33.87 to 28.01, p=0.001), no difference in TA muscle or subcutaneous tissue thickness Significant decrease in RF cross-sectional view grey-scale standard deviation (31.4 to 28.73, p=0.041) and significant increase in subcutaneous RF tissue thickness (1.13 to 1.41cm, p=0.033), no difference in RF muscle thickness or mean grey-scale value No changes in any muscle features of adductor digiti minimi or biceps Following hospital discharge, only mean subcutaneous tissue thickness over all sites showed a significant reduction (n=4, 0,74 to 0.31cm, p=0.002); changes at individual muscle sites did not reach significance
Grimm et al [253]	Measurements performed between days 2-5, and day 14, after onset of severe sepsis or septic shock	Inter-image measurements of echogenicity demonstrated inter-rater ICC of 0.915 and intrarater ICC of 0.972. 75% of patients demonstrated a mean echotexture >1.5 (the maximum reported in a comparative non-matched healthy control group); a significant difference in mean muscle echotexture between patients and controls was found at both measurement time-points (both p<0.001); non-significant increase in mean echotexture grades in patients between measurement time-points (p=0.085); non-significant difference in comparison of echogenicity between proximal and distal muscles in patients at either measurement time-point; significant (p<0.001) tests for trend per visit and anatomical muscle region for echotexture score

Puthucheary et al [250]	Measurements performed on days 1, 3, 7 and 10 of ICU admission	Significant reduction in rectus femoris cross-sectional area from days 1 to 7 (-12.5% (95%CI -35.4 to 24.1%), p=0.002), with a continued decrease to day 10 (-17.7% (95%CI -25.9 to 8.1%), p<0.001); significant association seen between change in RF_{CSA} and ICU length of stay (p<0.001); increased organ failure correlated with change in RF_{CSA} (r^2=0,23, p<0.001); change in RF_{CSA} differed between patients with multi- and single-organ failure (day 3, -8.7% (95%CI -59.3% to 50.6% vs. -1.8% (95%CI -12.3% to 10.5%) respectively, p=0.03), day 7, -15.7% (95%CI -27.7 to 11,4% vs. -3.0% (95%CI -5.3 to 2.1%) p<0.001); change in RF_{CSA} greater in those with ≥4 failed organs (-20.3% (95%CI -34.7 to 17.5%)) vs. 2-3 failed organs (-13.9% (95%CI -25.7 to -9.8%)) (p<0.001) Change in RF_{CSA} at day 10 was negatively associated with serum bicarbonate, PaO_2:FiO_2 and Hb concentration at ICU admission (r^2=0.51, p<0.001) and positively associated with degree of organ failure, mean C-reactive protein level and total protein delivered during study period Age (odds ratio (OR) 1.05/yr, 95%CI (1.01-1.07/yr)), bicarbonate level at admission (OR 0.72mmol (95%CI 0.65-1.00mmol)), and PaO_2:FiO_2 (OR 0.88, 95%CI (0.87-0.97)) found to be associated with >10% loss in RF_{CSA} at day 10 Inter-observer agreement ICC 0.97 (n=21 patients), Bland Altman analysis demonstrated bias (SD) and 95% limits of agreement of 7 (37)mm^2 and -66.1 to +80.5mm^2

*only detail provided regarding peripheral skeletal muscle data in critically ill patients.

Abbreviations: MOF = multi-organ failure. MLT = muscle layer thickness. MLTD = muscle layer thickness difference. LOS = length of stay. ICU = intensive care unit. ICC = intraclass correlation coefficient. RF = rectus femoris. RF_{CSA} = rectus femoris cross-sectional area.

5.4 Discussion

The current systematic review identified and included seven studies evaluating the effect of critical illness on peripheral skeletal muscle architecture using ultrasound as the measurement tool. Each study assessed an independent general ICU population, with patients presenting with sepsis and multi-organ failure with an ICU length of stay of at least seven days. There were changes in a variety of muscle architecture parameters observed using ultrasound across a range of anti-gravity and non-gravity muscle groups, with ultrasound assessment demonstrating both clinical reliability and utility.

5.4.1 Significance of findings

Ultrasound data reported by all the studies included in this review demonstrated the negative effect of critical illness on peripheral skeletal muscle architecture. Despite this, meta-analyses of data were not possible due to the wide variation in muscle groups and architecture parameters assessed, the differing study protocols adopted, and the extent and clarity of data reporting. Hence consideration of the overall effects of confounding factors such as age, acuity of illness at ICU admission or nutritional management on muscle architecture during critical illness are also limited.

Five studies measured muscle thickness [81, 82, 86, 252, 254] with only two reporting illness severity using differing forms of APACHE scoring [86, 252], all with differing results. There was no consistent baseline adopted across these studies with muscle wasting occurring between actual time of ICU admission and the first measurement point potentially not captured. Furthermore, three of these studies analysed total muscle thickness which was calculated as the average across all muscle groups measured [82, 86, 254]. Individual variations in degree of muscle wasting could also have contributed to findings. In two studies where muscle thicknesses for individual muscle groups were reported, [81, 252], comparison was not made. These protocol and data presentation variations also limit consideration of whether the effects of critical illness vary across distribution of peripheral skeletal muscle. Muscle echogenicity increased in two studies,

although measured using different methods, reporting the presence of myopathic changes in the muscle occurring during critical illness possibly due to muscle oedema from capillary leak during acute sepsis and/or loss of the typically organized muscle architecture occurring during muscle breakdown [81, 253]. Data from muscle biopsy analysis (quadriceps vastus lateralis) on Days 1 and 7 of ICU admission confirm this, reporting muscle necrosis and macrophage cellular infiltrate [250].

No study investigated the relationship between muscle wasting in critically ill patients and functional outcome. Indeed, there are currently no defined minimum clinically important differences in terms of the threshold for muscle loss and functional outcome, even if the studies in the present systematic review achieved changes in muscle loss of statistical significance. Strength has been shown to correlate with peripheral muscle cross-sectional area in both healthy subjects, and patients with chronic cardiac and respiratory disease [73, 102, 256, 265] although there are few data for critically ill patients. In patients able to undergo peripheral muscle strength assessment using dynamometry, Baldwin *et al* [252] found significant correlations with relevant muscle group thickness ranging from weak to moderate. Ideally, contemporaneous measures of peripheral skeletal muscle force would validate ultrasound measures of muscle architecture, and which could then be mapped to levels of physical functional ability.

Interestingly, there were no studies reporting the measurement of fibre pennation angle, which in combination with anatomical cross-sectional area values provides data on physiological cross-sectional area, in turn associated with the force-generating capacity of a muscle [98]. However, as shown in *Chapter 4*, there is limited clinical advantage of assessing the complex measure of pennation angle and physiological cross-sectional area compared to the relatively simple measurement of anatomical cross-sectional area.

5.4.2 Technical considerations

Ultrasound measurements were feasible in all patients in all studies with the exception of two circumstances. Puthucheary *et al* [250] reported one patient

from their cohort was unable to complete assessment of rectus femoris cross-sectional area due to morbid obesity, and echotexture was not assessed in the diaphragm of patients in the study by Cartwright *et al* [81] as the muscle was too thin for accurate measurement. High reliability of the ultrasound technique in critically ill patients was evident in three of the studies included in the current review [250, 252, 253]. Furthermore, very low inter-observer variation has also been reported by Jorgensen and colleagues (Bland-Altman bias, -0.07cm^2, 95% limits of agreement, -0.188 to 0.048cm^2) [255] albeit as abstract data only.

All studies reported technical detail of ultrasound image acquisition including the make and model of machinery and the type of transducer employed. A number of studies measured similar muscle groups however variation was evident in level of detail provided for patient positioning during measurement and precise location on the muscle group for imaging. Whilst standardisation of protocols within studies provides internal validity for the use of ultrasound as a tool for monitoring change in muscle architecture, variation across studies precluded pooling of data to determine overall effect. Future consensus on the exact detail of ultrasound measurement for various muscle groups would facilitate consistency with its increasing clinical use.

Ultrasound findings all indicated superiority over measures of limb circumference, where performed, due to the confounding problem of subcutaneous oedema influencing accuracy of limb circumference data. Typically whilst muscle cross-sectional area or thickness decreased, limb circumference remained unchanged [82, 86, 254]. Furthermore, previous data has shown that ultrasound measures of peripheral skeletal muscle architecture correlated closely with data obtained via magnetic resonance imaging [84] or computed tomography [73] scanning modalities, supporting the use of ultrasound over other techniques that are more costly, time-consuming and which involve radiation. Although these data originate from healthy subjects and stable patients with chronic respiratory disease, they are nonetheless valuable as conducting similar comparative studies in critically ill patients has limited feasibility. However, additional investigation by Puthucheary *et al* [250] suggests some caution in interpretation of ultrasound data. In their cohort of critically ill patients a subset also underwent additional measures of

muscle wasting, namely muscle biopsy and quantification of protein to deoxyribonucleic acid (DNA) ratio. Ultrasound of muscle cross-sectional area was shown to underestimate muscle fibre cross-sectional area, but of more concern was that the greatest reduction was observed in the protein/DNA ratio over 10 days highlighting that ultrasound underestimated the actual loss in muscle mass. In this study differences in the muscle groups studied, in particular ultrasound measurement of quadriceps rectus femoris vs. fibre cross-sectional analysis and protein/DNA ratio of quadriceps vastus lateralis, were proposed explanations in part, for the variation in muscle loss. However, of more significance was that the protein/DNA ratio was unaffected by the water content of the muscle, which strongly supports the observation that ultrasound underestimates muscle loss as a consequence of muscle oedema. Investigation of muscle composition using grey-scale analysis may assist in determining the level of intramuscular fluid to provide a clinically applicable assessment of muscle quality which, as well as muscle quantity, should be reported in future studies, albeit further validation of echogenicity findings against data from MRI imaging is still required. Furthermore, the additional analyses undertaken by Puthucheary *et al* [250] were invasive, costly, required expertise for conduct, analysis and interpretation and were only feasible in a very select patient group. As previously described, ultrasound demonstrated advantages over invasive testing in all these areas, and these data should not detract from the clinical utility of ultrasound provided clinicians are aware of the potential limitations that may exist in data acquired.

5.4.3 Critique of the method

This systematic review was conducted and reported in line with PRISMA guidelines [266]. Relevant search terms chosen aimed to identify studies where the primary intent was to evaluate changes in peripheral skeletal muscle architecture during critical illness using ultrasound. In this way reference to effects of critical illness on respiratory musculature, in particular the diaphragm, were excluded. However use of ultrasound as a technique for this purpose has been recently reported in two comprehensive reviews [273, 274], with a growing body of data documenting diaphragm atrophy during critical illness and the process of weaning from mechanical ventilation [81, 252, 275-277]. Notably two

of these studies, included in this review, assessed diaphragm muscle architecture contemporaneously with that of peripheral skeletal muscle [81, 252]. Baldwin *et al* [252] reported a significant reduction in peripheral skeletal muscle thickness and thickness/fat-free mass compared to the diaphragm in critically ill septic patients (where muscle thickness expressed as z-scores albeit exact values not reported). Cartwright *et al* [81] assessed muscle thickness and echotexture in a range of peripheral skeletal muscles, although as previously mentioned, grey-scale analysis was not possible on the diaphragm muscle. A significant increase in subcutaneous tissue when imaging the diaphragm was evident between days 1 and 14 of critical illness (0.88 to 1.03cm, p=0.024), although diaphragm thickness did not change. Diaphragm and peripheral skeletal muscle groups were not compared.

Furthermore studies involving change in peripheral skeletal muscle architecture as an outcome measure to determine effectiveness of an intervention were also excluded. The majority of these related to a number of randomised controlled trials of electrical stimulation to preserve muscle mass in critically ill patients [278-282], itself the topic of a recent, more focused systematic review [151]. However, that the search terms adopted in the current review failed to identify all studies reported by Parry *et al* [151], only serves to highlight the pragmatic limitations of robustly identifying all potential interventional trials where peripheral skeletal muscle architecture measured using ultrasound could be an outcome measure. Prior knowledge of the intervention would be required to facilitate database searching using relevant indexing terms.

Only studies based within the ICU were included, focusing on the early stages of critical illness. Despite this, two sources of excluded evidence (one only available in abstract form), and one included study, reported use of ultrasound measurements of peripheral skeletal muscle architecture following ICU discharge on the ward [283], and up to 6 [81] and 12months [83] post discharge, reporting benefit of the technique for longitudinal monitoring of the trajectory of recovery of peripheral skeletal muscle architecture following critical illness. This could further assist in identifying the optimum time for delivery of exercise-based rehabilitation interventions following hospital discharge.

Data available in abstract form only were excluded from this review due to the lack of detail provided in these summaries. On further inspection and following attempted author contact, only one abstract remained excluded that contained potentially relevant data of interest to the review question. Mampilly *et al* [284] reported significantly reduced rectus femoris muscle cross-sectional area values for critically ill patients (n=5) compared to healthy subjects, but similar to those found in ambulatory patients with chronic obstructive pulmonary disease.

In categorising the study design for included studies, this review adhered to a recognized published classification algorithm [269]. However, the majority of included studies were found to be non-comparative case series. Whilst this is perhaps not wholly unsurprising, given the nature and purpose of the review investigating the clinical utility of a measurement technique such as ultrasound rather than the effectiveness of a particular intervention, there was no tool available for assessing the quality of these studies which is a limiting factor to their methodological robustness.

5.4.4 Future considerations

Currently, there is no gold standard for the measurement of peripheral skeletal muscle architecture using ultrasound, and this review demonstrated wide variation in reporting and methodology of a variety of parameters examined in the critical illness population. Further work is necessary to determine uniformity of technical application. Minimum reporting detail would include make and model of machine, probe specification, image acquisition settings, and precise description of patient position and location on the muscle for measurement. In addition detail on online and offline image analysis should be provided. For future studies, in particular multi-site trials, where ultrasound measurements were to be used to collect data, establishing acceptable intra- and inter-observer reliability will be important. This would in turn facilitate determining a clinically important difference in muscle architecture parameter. In *Chapter 4*, Bland Altman analysis revealed quite wide variation for some critically ill patients even between two experienced clinicians, and hence this must be accounted for when considering effect size in response to an intervention, or over time.

Inclusion of standard operating protocols as supplementary materials to publications would strongly facilitate future consensus on this. Building on this, expert consensus on adoption of a standardised 'checklist' of reporting items could be valuable for the literature. Future studies should also aim to determine the relationship between ultrasound measurements, both single and sequential measurements, and clinically relevant functional outcomes of the patient and the temporal change in the muscle itself.

5.5 Conclusion

This review has shown that ultrasound has increasing popularity as a tool for evaluating changes in peripheral skeletal muscle architecture during critical illness. Data can be acquired simply, easily and over sequential time points to fully track peripheral skeletal muscle loss. Ultrasound has a number of practical and clinical advantages which, when supplemented with data demonstrating high levels of reliability, confirm the clinical utility of the tool. Further investigation with regards to muscle composition using grey-scale analysis of images will assist in corroborating detailed muscle biopsy data. Furthermore, standardisation of the protocol of acquisition, such as measurement of cross-sectional area at 2/3 distance or 3/5 distance from the anterior superior iliac spine to the superior patellar border (*Chapter 4*) would permit future meta-analyses of data. This would allow detailed investigation of the influence of confounding factors associated with ICU management on alteration of peripheral skeletal muscle architecture during critical illness.

Chapter 6 Exercise-Based Rehabilitation Following Critical Illness: A Pilot Feasibility Randomised Controlled Trial

6.1 Introduction

The long-term consequences of critical illness are increasingly recognised. More recently, the constellation of physical, psychological and mental health impairment has been termed 'post intensive care syndrome' [125] with physical rehabilitation advocated in the management of the physical and functional deficit observed in survivors of critical illness. Although still limited, the data are increasing to support the use of early mobilisation interventions within the ICU [142, 154, 163, 164, 285] and following transfer to the ward [174, 177]. However, beyond hospital discharge, exercise-based rehabilitation tends to be more inconsistent in delivery with few randomised controlled data available [186]. Indeed three recent randomised controlled trials focussing on exercise-based rehabilitation from hospital to home demonstrated little or no clinical benefit [177, 179, 180]. Interestingly, none of these recent trials stratified patients by the presence of ICU-AW or peripheral muscle wasting as an inclusion criterion and thus the target population may have been less likely to benefit from the intervention.

In the UK, attention on rehabilitation practice spanning the continuum of recovery for ICU survivors has been driven by publication of national guidelines by the National Institute for Health and Care Excellence in 2009 (NICE CG83) [136]. Despite this, practical implementation of these recommendations has been restricted by both lack of evidence supporting this approach and limited detail outlining the type, intensity and frequency of any exercise-based rehabilitation programme.

6.1.1 Aims of study

The aim of this study was to conduct a pilot, feasibility exploration of a post hospital discharge exercise-based rehabilitation programme for survivors of critical illness with ICU-AW, to assess impact on a range of outcome including exercise capacity and health-related quality of life.

6.2 Methods

6.2.1 Study design

This was a pilot feasibility study adopting a randomised controlled trial (RCT) design investigating the physiological-centred and patient-centred effects of a sixteen-session, exercise-based rehabilitation programme delivered following hospital discharge in survivors of critical illness with intensive care unit-acquired weakness (ICU-AW). The trial was registered on an international trials registry (Clinical Trials, www.clinicaltrials.gov, NCT00976807). Outcomes included exercise capacity, health-related quality of life, measures of peripheral skeletal muscle size and strength, anthropomorphic data and physical function.

Patients were recruited following their admission to the general ICUs of St.Thomas' Hospital and King's College Hospital, two University of London teaching hospitals within an Academic Health Sciences Centre framework (60 beds in total). St.Thomas' Hospital is a regional severe respiratory failure centre, and King's College Hospital has a regional major trauma and neurosciences centre. Both hospitals also admit a mixed cohort of medical and surgical populations.

6.2.1.1 Observational study of clinically strong patients

This sub-study was designed to explore the trajectory of recovery of those patients without ICU-AW. For the purposes of this study these patients have been defined as 'clinically strong'. The aim of the study was to assess the suitability of using the diagnosis of ICU-AW (MRC-SS <48/60) as an inclusion criterion into post critical illness rehabilitation programmes. This sub-group of patients were followed-up in a similar manner as the standard treatment arm of the trial as part of an embedded observational cohort study.

6.2.2 Participants

Patients were eligible for inclusion into the RCT if they met the following criteria:

1. Aged ≥18years

2. Received mechanical ventilation (MV), either via endotracheal tube or non-invasive mask for ≥48hours during ICU admission
3. Demonstrated ICU-AW as measured by MRC-SS <48/60 at ICU discharge
4. Glasgow Coma Scale 15/15, and Abbreviated Mini Mental Test ≥8/10
5. Expected survival to hospital discharge
6. Demonstrated sufficient mobility to participate in an exercise-based rehabilitation programme at hospital discharge

Patients were excluded from the study if they met the following criteria:

1. Terminal/palliative prognosis
2. Unstable coronary artery syndrome or other severe cardiac disease
3. Acute limb amputation
4. Peripheral vascular disease awaiting revascularisation
5. Acute stroke or other neurological disease
6. Musculoskeletal disabling condition precluding ability to exercise
7. Psychiatric illness
8. Requirement for ongoing renal dialysis
9. Extra-contractual ICU referral (if unable to attend the hospital twice-weekly if randomised to receive the intervention)
10. Extensive medical co-morbidity precluding regular participation in exercise
11. Existing rehabilitation pathway in place e.g. post cardiac surgery, chronic respiratory disease

6.2.2.1 Observational study of clinically strong patients

These patients were required to meet the same inclusion criteria except with regard to MRC-SS at ICU discharge. Instead, these patients were considered as 'clinically strong' demonstrating an MRC-SS ≥48/60. Similar exclusion criteria applied to this observational cohort of patients, with the exception of geographical residence. As these patients would be managed within the study as per the standard treatment arm of the RCT, and only be required to return to the hospital for one completion assessment at three months, they were eligible for inclusion if they reported they would be prepared to attend.

6.2.3 Screening and recruitment

All patients who had received mechanical ventilation during their ICU admission were screened for potential eligibility into either the RCT or observational cohort study prior to ICU discharge. Screening occurred over six sessions per week depending on the availability of the researcher (BC) at each study site. Patients meeting inclusion criteria were approached to discuss the study prior to their ICU discharge and provided with a patient information sheet. Consenting patients were asked to complete a consent form, a copy of which was given to the patient and a further copy filed in their medical notes.

6.2.4 Randomisation and masking for the randomised controlled trial

Subsequent to consent, patients were allocated to treatment groups (standard treatment or intervention) through the Mental Health and Neuroscience Clinical Trials Unit (London, UK). Treatment allocation to either the intervention arm or standard treatment (control) arm was undertaken independently of the trial team. The first fifteen participants randomised were allocated with straightforward simple randomisation. Thereafter, and following review of the demographic and anthropometric data identified by the trial team, important cofounding variables were identified and allocation was stratified by gender (M:F), APACHE II score (<18, ≥18), duration ICU LOS (≤21 days, >21 days), study site (King's College Hospital, St.Thomas' Hospital), and MRC-SS (37-48, ≤36) with computer-generated probabilistic minimisation. The minimisation factor of ICU LOS was amended from ≤7 days;>7 days following interim review of the initial 17 patients recruited and their randomisation characteristics.

6.2.5 Blinding

Once notified of treatment allocation by the Clinical Trials Unit, the researcher (BC) informed the patient and relevant clinicians. As with many therapy trials, and in particular given the pilot nature of the current trial, patients, therapists, and doctors were not blinded to treatment allocation. Furthermore it was impractical to blind the researcher (BC) who was responsible for all aspects of trial conduct

including screening, consent, baseline and completion assessment, follow-up and intervention delivery.

6.2.6 Screening for awakening and assessment of peripheral muscle strength

Conscious level of patients in both the randomised controlled trial and observational cohort study was determined using the Richmond Agitation Sedation Scale (RASS) [49], which is an ordinal scale ranging from -5 (unrousable) to +4 (combative behaviour), and including 0 (alert and calm) and a nominal 'A' indicating the subject is asleep. A score of -1 (drowsy) to +1 (restless) was considered indicative of wakefulness.

Awake patients were then required to demonstrate positive response to four simple one-stage commands including 'open and close your eyes', 'stick out your tongue' and 'squeeze my fingers'. Successful completion of these commands was followed by muscle strength assessment using the MRC-SS which is a 6 point grading scale ranging from 0 (no visible contraction) to 5 (normal power) applied to six upper and lower limb muscle groups bilaterally [35] (Chapter 2.3). ICU-AW was defined as an MRC-SS <48/60 [30, 36, 40, 41, 240]. This protocol for screening for awakening and assessment of peripheral muscle strength was in keeping with previous reported studies investigating the MRC-SS and ICU-AW [11, 36, 37],

6.2.7 Outcome measures

A range of outcomes measures were assessed at baseline (hospital discharge) and at three-month completion (Figure 6-1) including:

i) Anthropometric data
ii) Exercise capacity - Incremental Shuttle Walk Test (ISWT) and Six Minute Walking Test (6MWT)
iii) Health-related quality of life (HRQL) – Short Form-36 Physical (SF-36 PCS) and Mental (SF-36 MCS) Component Scores and Hospital Anxiety and Depression Scale (HADS)

iv) Peripheral skeletal muscle strength - quadriceps maximum voluntary contraction (QMVC) and handgrip dynamometry

v) Peripheral skeletal muscle size - quadriceps rectus femoris cross-sectional area (RF_{CSA})

vi) Physical function - SF-36 Physical Function domain (SF-36 PF), Barthel scale, Timed Up And Go (TUAG), Sit-to-Stand 5 (STS-5)

Details for all assessment measures can be found in *Chapter 2*.

6.2.8 Standard treatment arm of the randomised controlled trial

Patients randomised to the standard treatment arm received a weekly telephone call from the researcher (BC) to monitor general progress of recovery. Although this was not necessarily in keeping with routine standard care, this was mandated by the ethical review board. No specific advice on exercise rehabilitation was provided.

6.2.9 Intervention arm of the randomised controlled trial

Given the absence of detailed guidance or existing data on optimum structure, content, format and delivery of post hospital discharge rehabilitation for survivors of critical illness [186], the exercise-based rehabilitation programme (EBRP) intervention was modelled closely on current pulmonary rehabilitation (PR) programmes in operation at both recruitment sites and part of the established clinical and research rehabilitation programmes, widely studied within the author's research group [187, 188]. The clinical programmes have been established based on national and international guidelines [204, 286, 287].

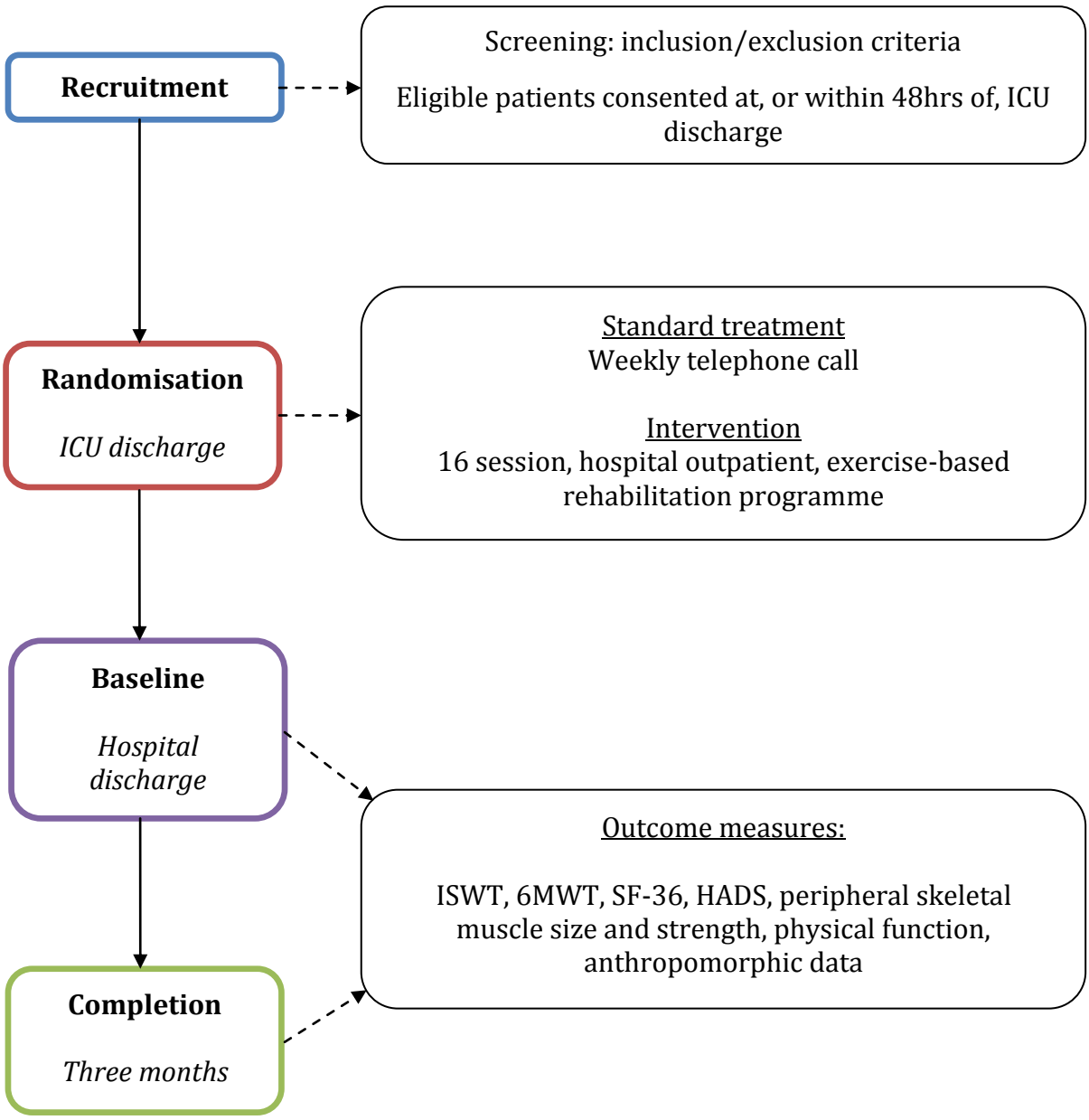


Figure 6-1 Schematic outline of the randomised controlled trial pathway

Abbreviations: ISWT = Incremental Shuttle Walk Test. 6MWT = Six Minute Walk Test. SF-36 = Short-Form 36. HADS = Hospital Anxiety and Depression Scale.

6.2.9.1 EBRP delivery format

The EBRP was a sixteen-session hospital-based, outpatient intervention conducted at both study sites, in which patients exercised under supervision and independently, accompanied by a printed manual containing all warm-up, cool-down and individually prescribed exercises. For pragmatic and logistical reasons, the programme was run in tandem with existing PR programmes for patients with

chronic respiratory diseases, in operation at each study site. Patients commenced participation in the programme within two weeks of hospital discharge, and transport was provided for patients to attend. Successful completion was defined *a priori* as attendance at ≥50% of sessions.

6.2.9.2 EBRP structure

The EBRP consisted of 16 sessions scheduled to run twice-weekly. Each session lasted one hour (40minutes exercise including warm-up and cool-down), and the programme was 'rolling' in structure i.e. patients could start and finish the EBRP at any point in time. Typically there were 1-2 patients enrolled at any time, supervised by one highly experienced critical care and rehabilitation clinical specialist physiotherapist (BC). Patients exercised according to their own individualised plan.

6.2.9.3 EBRP content

The EBRP included cardiovascular, strength, balance and functional exercises. Specifically, cardiovascular exercises included step-ups, treadmill, cross-trainer and static cycling; strength exercises included those for upper and lower limb muscle groups including quadriceps, biceps and triceps, utilising weights and theraband (exercise bands) for resistance work; balance activity included static and dynamic exercises, and functional activities included sit-to-stand and walking. Exercises were tailored to individual patients depending on clinical assessment and patient-specific goals, and could include some or all of the aforementioned. In this way both clinician judgement and patient input determined methods of exercise prescription. More objectively, exercise prescription was based on the results of walking tests for cardiovascular (for walking speed), and use of the repetition maximum (RM) principle for strength (initial weight, 80% 10RM).

Target Borg scores for perceived exertion (level 3-5, moderate to severe) were used to monitor exercise intensity during sessions. In addition, and depending on individual patient clinical status, oxygen saturation (SpO_2) and heart rate (HR)

levels were also used. At all times, patient verbal feedback and clinician judgement of patients was used to ensure patient safety whilst exercising.

The EBRP contained an informal education component, where patients were invited to participate in sessions covering management of breathlessness, benefits of exercise, nutrition and energy conservation, that were running as part of the main PR programme, and which could be relevant to them. In addition the researcher was available to offer specific 1:1 education and advice on patient-specific matters, or organise onward referral where necessary to appropriate multidisciplinary healthcare colleagues.

Supplementary to the two supervised exercise sessions per week, patients were strongly encouraged to undertake one independent session using a leaflet containing their individual exercises, and to record this in an exercise diary. Adherence to this independent exercise session was not formally monitored by the researcher.

6.2.9.4 EBRP evaluation

In addition to the outcome measures described above for EBRP evaluation, patients were asked to complete acceptability questionnaires at the end of their programme to obtain patient-specific feedback.

6.2.10 Observational cohort study of 'clinically strong' patients

Patients recruited to the observational cohort study of 'clinically strong' patients without ICU-AW (MRC-SS >48/60) were followed-up in a similar manner as the patients in the standard treatment arm of the trial. These patients received weekly telephone calls from the researcher (BC) during the three month follow-up period.

6.2.11 Statistical analysis

All data are expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) as appropriate. Paired t-tests or Wilcoxon signed rank

tests for parametric and non-parametric data respectively were performed to determine differences between baseline and completion for standard treatment and intervention arms of the RCT, and for the observational cohort study. To establish differences between standard treatment and intervention arms of the RCT, unpaired t-tests or Mann-Whitney tests were applied for parametric and non-parametric data respectively. These same tests were applied to determine differences between the randomised cohort overall (with ICU-AW) and the observational cohort study ('clinically strong'), however only outcomes related to physical performance were selected for comparison based on the rationale that these had the potential to be more influenced by degree of global peripheral skeletal muscle strength.

6.3 Results

6.3.1 Randomised controlled trial

Patients were recruited between February 2010 and May 2012 with follow-up completed by August 2012. Patient flow-through the trial is described in the trial Consolidated Standards of Reporting Trials (CONSORT) diagram (Figure 6-2). A large proportion of potentially eligible patients were excluded (n=743). Table 6-1 details the frequency of occurrence of meeting the predefined inclusion and exclusion criteria at ICU discharge.

Twenty patients consented and were randomised, ten each into the standard treatment and intervention arms of the trial. Baseline characteristics of the cohort are reported in Table 6-2, with no differences between standard treatment and intervention arms for any factor (all p=ns). Median (IQR) MRC-SS for the trial patients with ICU-AW was 43.0 (39.0-44.8).

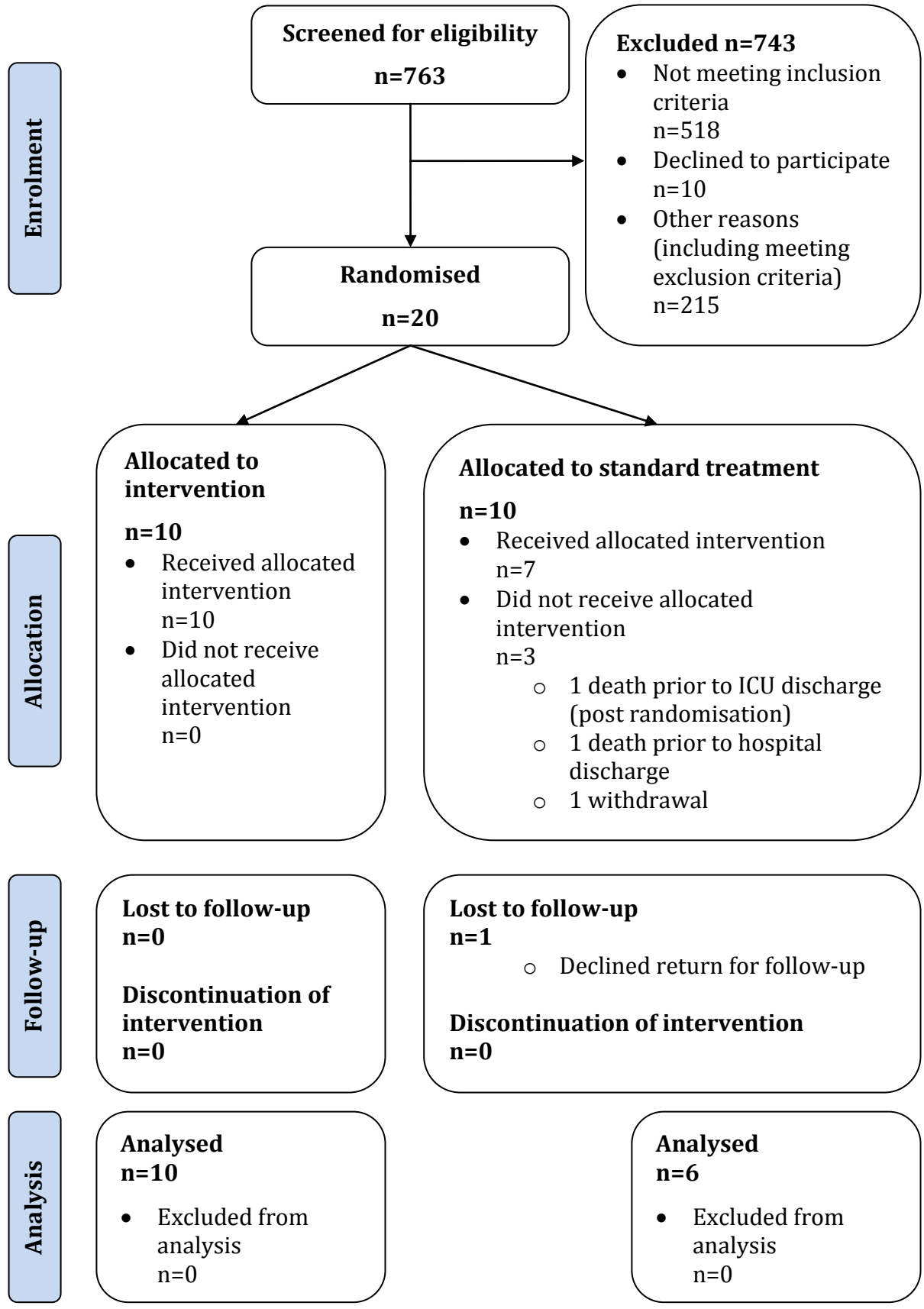


Figure 6-2 CONSORT diagram detailing patient flow-through within the randomised controlled trial

Abbreviations: ICU = intensive care unit

Table 6-1 Factors accounting for ineligibility into the randomised controlled trial

Factor	Frequency of occurrence (%)	Classification
Ventilation ≥48hrs	294 (39.6)	Inclusion criterion not met
Extra-contractual tertiary referral	185 (24.9)	Exclusion criterion met
MRC-SS <48/60	132 (17.8)	Inclusion criterion not met
Existing rehabilitation pathway	131 (17.6)	Exclusion criterion met
Sufficient mobility	97 (13.1)	Inclusion criterion not met
ICU admission ≥48hrs	95 (12.8)	Inclusion criterion not met
Expected survival to hospital discharge	93 (12.5)	Inclusion criterion not met
Palliative/terminal prognosis	89 (12.0)	Exclusion criterion met
Complex medical co-morbidity	82 (11.0)	Exclusion criterion met
Disabling condition precluding exercise	80 (10.8)	Exclusion criterion met
Unstable cardiac diagnoses	75 (10.1)	Exclusion criterion met
Neurological diagnoses	64 (8.6)	Exclusion criterion met
Impaired Glasgow Coma Scale	42 (5.7)	Exclusion criterion met
Psychiatric diagnoses	42 (5.7)	Exclusion criterion met
Ongoing renal haemodialysis	32 (4.3)	Exclusion criterion met
Acute limb amputation	13 (1.7)	Exclusion criterion met
Acute peripheral vascular disease	5 (0.7)	Exclusion criterion met
Age >18years	4 (0.5)	Inclusion criterion not met

Data are presented as n (%), and report frequency of reported occurrence of each criterion, therefore total percentages exceed 100%. n=743. Multiple factors could apply per patient.

Abbreviations: MRC-SS = Medical Research Council Sum-score. ICU = intensive care unit.

Table 6-2 Baseline characteristics for standard treatment and intervention arms of the randomised controlled trial

Characteristic	Standard Treatment Group (n=10)	Intervention Group (n=10)
Age (years)	68.5 (64.3-78.0)	63.0 (46.8-71.8)
Gender (M:F)	3:7	3:7
ICU diagnosis* (%)		
Medical	6 (60)	7 (70)
Surgical	4 (40)	3 (30)
Chronic disease* (%)		
Respiratory	4 (40)	7 (70)
Cardiac	5 (50)	4 (40)
Other#	5 (50)	3 (30)
APACHE II	23.5 (21.0-30.3)	24.5 (18.8-29.5)
SOFA (ICU admission)	12.0 (7.5-14.3)	9.5 (8.0-12.5)
Duration MOF (days)	10.5 (5.8-13.3)	9.5 (6.8-15.3)
MV (days)	11.2 (6.0-15.2)	9.3 (6.0-13.9)
CPAP (days)	2.0 (0.3-4.6)	1.3 (0.04-6.9)
Tracheostomy (%)	3 (30)	5 (50)
ICU LOS (days)	13.0 (9.8-20.5)	14.5 (7.0-17.8)
CC LOS (days)	18.0 (13.8-36.5)	17.5 (9.0-27.3)
Ward LOS (days)	27.5 (10.0-46.3)	20.0 (10.0-43.0)
Hospital LOS (days)	47.5 (26.5-68.5)	39.0 (22.3-66.5)

Data are presented as median (interquartile range) or n(%). *ICU diagnosis and chronic disease indicates frequency of occurrence. Patients could present with more than one comorbidity. #Other chronic comorbidities included diabetes mellitus, osteoarthritis/gout, stable chronic renal disease.

Abbreviations: ICU = intensive care unit. APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = Sequential Organ Failure Assessment. MOF = multi-organ failure. MV = mechanical ventilation. CPAP = continuous positive airway pressure. LOS = length of stay. CC = critical care.

6.3.1.1 Results of outcome measures of patients with intensive care unit-acquired weakness in the randomised controlled trial

Table 6-3 summarises the results of the outcome measures investigated. There were no significant differences between standard treatment and intervention groups at baseline, completion or in degree of change for any outcome measure (all p=ns and therefore not reported). A wide range of variability in results was evident as demonstrated by the size of interquartile ranges. For measures where minimum clinically important difference (MCID) data were available, albeit these data are established for chronic respiratory disease, both groups improved beyond these values of 47.5m for the ISWT [209], 54m for the 6MWT [213] and 10 points

for the SF-36 PF domain [226, 227]. However, there were no patients that achieved their predicted values for 6MWT at completion [288]. Median predicted 6MWT for the cohort was 490.1 (459.8-536.5)m, and percent predicted 6MWT achieved was 66.4 (46.2-89.1)%. There was no evident trend across outcome measures, for whether standard treatment or intervention group showed numerically more positive results.

At hospital discharge, median (IQR) MRC-SS of the trial cohort was 56.0 (52.0-58.0), and at completion, 60.0 (56.0-60.0) indicating that these patients no longer had ICU-AW as measured using the MRC-SS tool for diagnosis (<48/60).

Table 6-3 Results of outcome measures used to evaluate intervention effectiveness in the randomised controlled trial

Outcome measure	Standard treatment group (n=6)			Intervention group (n=10)		
	Baseline	**Completion**	**Change from baseline**	**Baseline**	**Completion**	**Change from baseline**
ISWT (m)	20.0 (10.0-60.0)	190.0 (70.0-355.0)	170.0 (40.0-315.0)	55.0 (7.8-120.0)	200.0 (132.5-340.0)	115.0 (-2.5-237.5)
6MWT (m)	150.0 (100.5-207.0)	335.0 (177.5-455.0)	185.0 (40.0-285.0)	180.0 (125.0-221.5)	328.5 (230.0-393.8)	140.0 (35.8-210.3)
SF-36 PCS (/100)	20.6 (19.4-33.3)	42.3 (27.9-47.6)	11.0 (4.3-28.3)	29.8 (24.1-33.2)	33.2 (23.8-45.4)	1.8 (-6.8-15.9)
SF-36 MCS (/100)	50.9 (35.6-57.8)	45.6 (34.3-54.7)	-11.4 (-19.0-19.1)	31.6 (28.6-49.1)	53.4 (39.5-58.8)	14.3 (-3.2-26.7)
SF-36 PF (/100)	7.5 (3.8-31.3)	37.5 (17.5-72.5)	15.0 (0.0-67.5)	15.0 (5.0-22.5)	40.0 (17.5-76.3)	22.5 (-5.0-60.0)
HADS total (/42)	14.0 (9.0-20.0)	6.5 (5.5-10.3)	-4.5 (-13.3- - 2.5)	13.0 (7.0-19.0)	9.0 (3.5-10.3)	-6 (-9.3- -2.8)
HADS anxiety (/21)	6.0 (1.5-11.5)	4.0 (0.8-6.0)	0.0 (-7.0-0.0)	7.0 (4.5-9.3)	4.0 (1.8-5.5)	-3.5 (-5.0--1.3)
HADS depression (/21)	8.5 (7.3-10.0)	2.5 (2.0-8.0)	-4.5 (-6.3--1.8)	5.5 (2.8-11.0)	4.5 (1.0-7.3)	-1.5 (-3.3-2.0)
QMVC (kg)	17.7 (16.2-20.7)	23.7 (17.8-36.7)	6.0 (1.6-16.0)	10.0 (6.6-24.6)	14.0 (8.2-26.3)	2.1 (0.8-4.5)
RF_{CSA} (mm^2)	395.0 (343.0-487.1)	497.5 (410.6-673.6)	61.7 (36.5-261.5)	241.3 (238.3-296.3)	487.3 (344.0-519.0)	222.7 (102.7-249.0)
Handgrip (kg)	17.0 (14.0-22.0)	22.0 (17.5-28.5)	3.5 (2.0-11.3)	22.0 (9.0-22.0)	24.0 (18.0-30.0)	8.0 (4.0-9.0)
Barthel (/100)	82.5 (75.0-95.0)	100.0 (88.8-100.0)	10.0 (2.5-25.0)	87.5 (65.0-96.3)	100.0 (82.5-100.0)	7.5 (0.0-21.3)
TUAG (s)	25.0 (17.3-34.0)	12.5 (8.0-19.0)	-11.5 (-25.5-0.8)	18.0 (13.5-125.0)	10.0 (7.3-41.5)	-7.0 (-86.3--4.0)
STS-5 (s)	23.0 (19.8-30.5)	17.3 (14.3-20.0)	-3.8 (-16.3--0.8)	17.5 (14.9-27.3)	13.0 (9.3-26.5)	-2.3 (-17.3-8.6)
FFM (kg)	51.8 (34.6-59.9)	43.6 (34.4-62.9)	2.3 (-2.3-4.7)	45.1 (38.4-55.1)	49.7 (42.3-51.3)	0.6 (-3.5-5.1)
FFMI (kg/m^2)	18.3 (13.0-19.7)	15.5 (14.1-20.7)	0.7 (-0.8-1.6)	17.4 (13.4-19.9)	16.7 (16.0-19.6)	0.3 (-1.3-1.6)

Data are presented as median (interquartile range). Handgrip, n=7 for intervention group due to patient inability to perform the test. QMVC, n=3 for the control arm and n=4 for the intervention arm due to death or withdrawal prior to assessment, inability to perform measure, and time permitting for assessment due to patient clinical commitments. RF_{CSA}, n=4 for control arm n=3 for the intervention arm due to death or withdrawal prior to assessment, time permitting for assessment due to patient clinical commitments and image quality. TUAG and STS-5, n=5 and 4 respectively for intervention group due to subsequent protocol amendments including these measures, inability to perform the measure, and time permitting for assessment.

Abbreviations: ISWT = Incremental Shuttle Walk Test. 6MWT = Six Minute Walking Test. SF-36 PCS = Short Form-36 Physical Component Score. SF-36 MCS = Short Form-36 Mental Component Score. SF-36 PF = Short Form-36 Physical Function domain. HADS = Hospital Anxiety and Depression Scale. QMVC = quadriceps maximum voluntary contraction. RF_{CSA} = rectus femoris cross-sectional area. TUAG = Timed Up And Go. STS-5 = St to Stand 5 times. FFM = fat-free mass. FFMI = fat-free mass index.

6.3.1.2 Adherence to the intervention

Of the ten patients randomised to receive the EBRP, eight successfully completed the programme (attending ≥50% of sessions). Median (IQR) number of sessions attended was 16.0 (9.3-16.0). One patient unable to complete the programme attended only one session due to recurrent chest infections, and a subsequent reluctance to continue with the intervention. The second patient failing to complete the programme attended seven sessions, and was unable to continue participation due to a general deterioration in health that was related to a separate illness diagnosis which was later confirmed as Addison's disease. For two of the eight patients who successfully completed the intervention, reasons for not attending the full sixteen sessions included seasonal chest infections, family circumstances and separate clinical appointments necessitating hospital attendance.

Within each session of the EBRP, there was potential for patients to exercise for 25 minutes (40minutes less warm-up and cool-down time), albeit this was also dependent on time taken for individual patients to move between exercise stations, which in itself could constitute an exertive activity (although not formally monitored). On average, patients exercised for a median (IQR) of 21.9 (20.9-23.4)minutes per session. Excluding non-completers did not change this value (median (IQR) 21.9 (21.0-23.2minutes/session)). There was insufficient documentation of independent unsupervised exercise sessions undertaken by participants for formal analysis.

Patients attended an average of 5 education sessions during the programme, with subject topics varying for each patient. Individual advice or education provided by the researcher was harder to quantify and analyse in a standardised format.

6.3.1.3 Adverse events during the trial period

No adverse events occurred during any of the exercise-based rehabilitation sessions. One patient in the intervention arm was admitted to hospital for investigation of cardiac symptoms occurring outside of the programme and noted

as unrelated to exercise participation. On discharge this patient was medically approved to resume full participation in the programme.

6.3.1.4 Patient-reported acceptability of the intervention

Six of the eight patients successfully completing the EBRP, completed a simple acceptability questionnaire asking for opinion on experience of participation. All six patients reported that overall, they were 'very satisfied' with the programme. When asked in greater detail regarding the exercise component, the following responses to these statements were noted:

1) Attending the exercise programme helped recovery from my illness
   66.7% strongly agree, 33.3% agree
2) I have a clear picture of how exercise will help my fitness
   66.7% strongly agree, 33.3% agree
3) I have a clear picture of how fitness will help in daily activities of my life
   66.7% strongly agree, 33.3% agree
4) I feel confident doing exercise
   66.7% strongly agree, 33.3% agree
5) I worry that exercise may be harmful to me
   33.3% strongly disagree, 66.7% disagree
6) I felt very stressed doing the exercise
   33.3% strongly disagree, 66.7% disagree
7) I found the visits to the hospital too tiring
   50% strongly disagree, 33.3% disagree, 16.7% agree
8) The exercise has not helped me
   66.7% strongly disagree, 33.3% disagree

Participants had the opportunity to attend education sessions that they felt relevant to them (noting that the intervention ran in tandem with an existing pulmonary rehabilitation programme for patients with chronic respiratory disease), and were also able to ask the researcher (BC) for any specific advice, information or guidance they required at any time. All participants attended at least four of the "formal" education sessions covering topics such as

breathlessness, energy conservation, smoking cessation and diet. One participant was unable to attend any of these sessions due to additional clinical appointments.

When responding to the following statements regarding level of satisfaction, participants were asked to consider the "formal" and individual education they had received:

1) The way the information was presented:
   16.7% very satisfied, 66.7% satisfied, 16.7% unable to comment (UTC)
2) The information given:
   16.7% very satisfied, 66.7% satisfied, 16.7% UTC
3) The opportunities you had to discuss any concerns:
   16.7% very satisfied, 66.7% satisfied, 16.7% UTC
4) The way the staff answered your questions:
   33.3% very satisfied, 50% satisfied, 16.7% UTC
5) The range of education topics covered:
   16.7% very satisfied, 50% satisfied, 16.7% neither, 16.7% UTC

The following qualitative comments were also reported in the acceptability questionnaires:

> *"...disappointed the discussions were mostly about COPD. Others were there – including myself – were recovering from other conditions. And so these discussions did not benefit me at all."*

> *"...I would have liked a speaker on my condition to help me to learn more. I don't think there is any need to change the exercise programme, I felt it worked very well for me."*

> *"...The exercise has helped me a lot. I feel much better for doing it, also all the staff were very helpful and very caring. I would recommend this to anybody who has problems with their breathing, it has been a joy working with a nice group of people."*

6.3.2 Observational cohort study of 'clinically strong' patients

Of the 743 patients excluded from the RCT, 132 failed to meet the inclusion criterion of demonstrating an MRC-SS <48/60 i.e. a diagnosis of ICU-AW. Of these,

21 were eligible and consented to participate in the observational cohort study of those 'clinically strong' patients (MRC-SS ≥48/60). One patient was withdrawn due to medical management during the hospital stay and did not complete any baseline testing. Participant flow-through is presented in Figure 6-3 with baseline characteristics for the cohort reported in Table 6-4. Median (IQR) MRC-SS for the observational cohort at enrolment at ICU discharge was 56.5 (53.3-59.8).

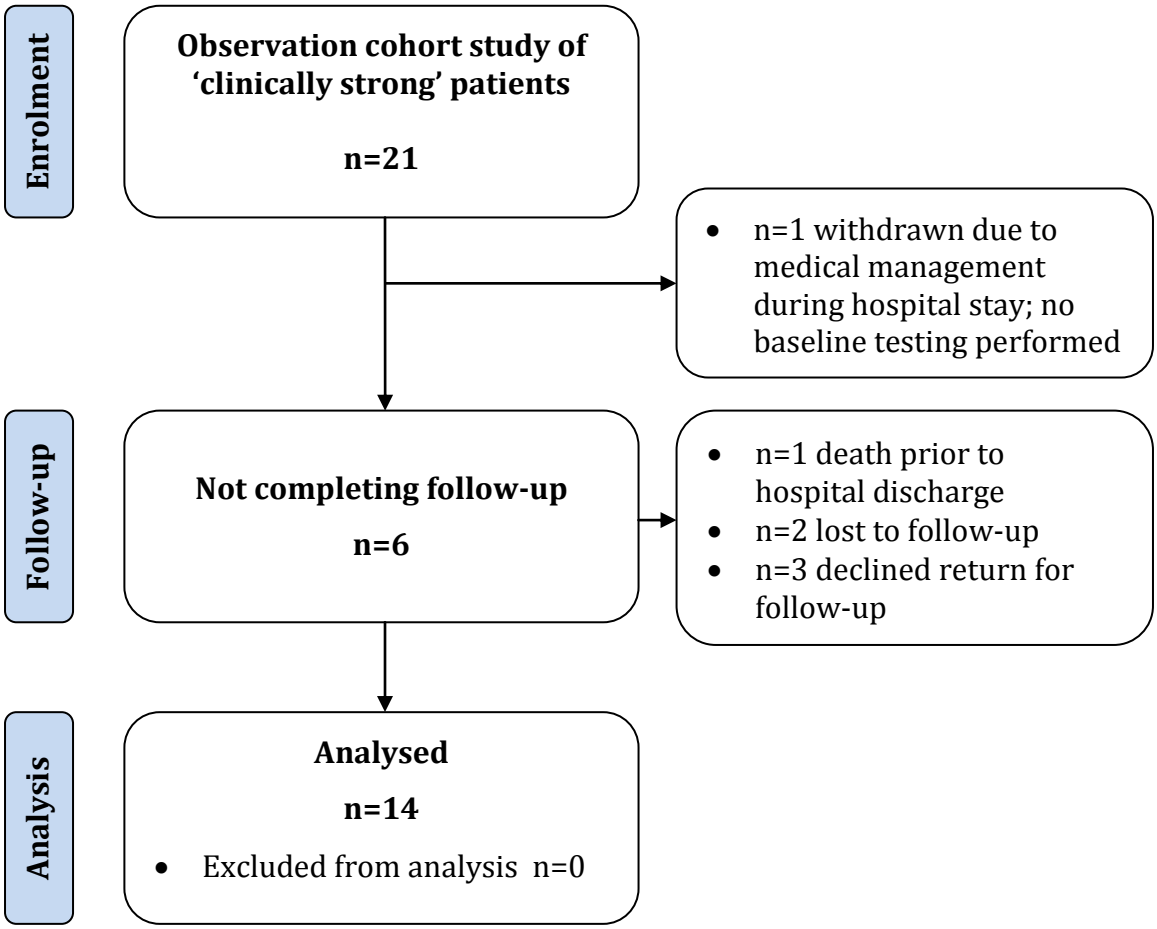


Figure 6-3 Flow-diagram detailing participant flow through observational study of clinically strong patients

Abbreviations: MRC-SS = Medical Research Council Sum-score

6.3.2.1 Results of outcome measures of clinically strong patients

The results for the observational cohort study of 'clinically strong' patients are presented in Table 6-5. As evident in the randomised cohort, large interquartile

ranges indicated high variability in results. Significant improvements were evident for both measures of exercise capacity (ISWT and 6MWT) beyond minimum clinically important differences for each test [209, 213]. However, median predicted 6MWT distance at completion for this cohort was 552.0 (480.2-621.6)m and median percent predicted distance achieved was 74.4 (58.0-93.5)%. There were significant improvements observed in health-related quality of life (SF-36 PCS and MCS), physical function (SF-36 PF domain, TUAG and STS-5), QMVC and RF_{CSA}. Change in SF-36 PF domain also exceeded the previously reported 10-point MCID [226, 227]. Change in Barthel score approached significance, although this cohort of patients was already highly functioning at baseline with maximum scores evident in some patients. Median (IQR) MRC-SS for the observational cohort at hospital discharge was 60.0 (57.0-60.0) and at completion, 60.0 (60.0-60.0).

Table 6-4 Baseline characteristics of observational cohort of 'clinically strong' patients

Characteristic	Observational cohort (n=21)
Age (years)	63.0 (49.5-70.0)
Gender (M:F)	16:5
ICU diagnoses* (%)	
Medical	15 (71.4)
Surgical	6 (28.6)
Chronic disease* (%)	
Respiratory	7 (33.3)
Cardiac	7 (33.3)
Other#	10 (47.6)
APACHE II	17.0 (12.5-19.5)
SOFA (ICU admission)	10.0 (7.5-12.0)
Duration MOF (days)	9.0 (3.5-14.5)
MV (days)	9.0 (4.3-20.4)
CPAP (days)	1.5 (0.4-2.6)
Tracheostomy (%)	8 (38.1)
ICU LOS (days)	10.0 (6.5-27.0)
CC LOS (days)	13.0 (10.0-37.0)
Ward LOS (days)	13.0 (6.5-19.5)
Hospital LOS (days)	30.0 (19.5-47.5)

Data are presented as median (interquartile range) or n (%).). *ICU diagnosis and chronic disease indicates frequency of occurrence. Patients could present with more than one comorbidity. #Other chronic comorbidities included diabetes mellitus, osteoarthritis/gout, stable chronic renal disease.

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = Sequential Organ Failure Assessment. MOF = multi-organ failure. ICU = intensive care unit. LOS = length of stay. MV = mechanical ventilation. CPAP = continuous positive airway pressure. CC = critical care.

Table 6-5 Results of outcome measures for the 'clinically strong' observational cohort study

Outcome measure	Baseline	Completion	Change	p
ISWT (m)	80.0 (30.0-212.5)	365.0 (250.0-477.5)	265.0 (207.5-300.0)	0.0002
6MWT (m)	167.0 (60.0-293.5)	433.5 (318.3-481.0)	157.5 (131.3-321.3)	0.0002
SF-36 MCS (/100)	44.4 (34.9-52.6)	51.4 (43.1-57.2)	4.7 (-1.8-11.4)	0.03
SF-36 PF (/100)	40.0 (15.0-66.3)	70.0 (41.8-80.0)	23.5 (3.8-31.3)	0.003
HADS				
Total (/42)	10.0 (6.8-14.0)	9.0 (6.5-13.0)	0.5 (-3.3-4.5)	0.8
Anxiety (/21)	5.0 (3.0-7.5)	4.0 (2.8-8.3)	0.0 (-2.0-3.3)	0.7
Depression (/21)	5.5 (2.8-7.3)	5.5 (1.8-7.5)	1.0 (-2.5-3.3)	0.8
QMVC (kg)	17.0 (12.6-33.3)	28.4 (20.3-40.3)	9.9 (-0.2-16.1)	0.04
RF_{CSA} (mm^2)	477.3 (314.5-711.3)	526.1 (442.0-898.0)	100.0 (59.4-186.7)	0.01
Handgrip (kg)	20.0 (16.0-27.5)	25.0 (23.0-27.5)	5.0 (-2.5-9.0)	0.1
Barthel (/100)	97.5 (85.0-100.0)	100.0 (98.8-100.0)	0.0 (0.0-15.0)	0.06
TUAG (s)	14.8 (13.1-18.5)	8.0 (6.8-10.0)	-6.0 (-9.3--3.8)	0.002
STS-5 (s)	19.0 (10.8-26.0)	11.4 (8.9-17.5)	-3.5 (-11.0--0.5)	0.008
FFM (kg)	52.5 (38.8-58.9)	52.5 (40.4-64.8)	2.5 (-0.7-9.7)	0.13
FFMI (kg/m^2)	18.9 (12.9-20.2)	18.2 (13.8-22.3)	1.0 (-0.2-3.4)	0.1

Data are presented as median (interquartile range). n=14. Handgrip, n=13 due to presence of arterial line in dominant hand restricting test performance. p values derived from Wilcoxon signed rank test and reflect change from baseline to completion. QMVC, n=9 due to equipment failure and patient clinical commitments. RF_{CSA}, n=11 due to patient clinical commitments.

Abbreviations: ISWT = Incremental Shuttle Walk Test. 6MWT = Six Minute Walk Test. SF-36 PCS = Short Form-36 Physical Component Score. SF-36 MCS = Short Form-36 Mental Component Score. SF-36 PF = Short Form-36 Physical Function domain. HADS = Hospital Anxiety and Depression Scale. QMVC = quadriceps maximum voluntary contraction. RF_{CSA} = rectus femoris cross-sectional area. TUAG = Timed Up and Go. STS-5 = Sit to Stand 5 times. FFM = fat-free mass. FFMI = fat-free mass index.

6.3.3 Comparison between 'clinically strong' patients and those with ICU-AW

The comparison of baseline characteristics between the ICU-AW and 'clinically strong' patients are presented in Table 6-6. The proportion of males to females was greater in the observational cohort (p=0.005). Patients with ICU-AW were sicker at ICU admission, with significantly higher illness severity (APACHE II) scores than 'clinically strong' patients (23.5 (20.3-29.5) vs. 17.0 (12.5-19.5), p<0.0001) and furthermore these patients also experienced a significantly longer ward stay (23.5 (10.3-43.0)days vs. 13.0 (6.5-19.5)days, p=0.03), and a numerically greater, albeit not statistically significant, overall hospital admission (46.0 (25.0-61.8)days vs. 30.0 (19.5-47.5), p=0.2).

The comparison of outcomes between the ICU-AW and 'clinically strong' patients are summarised in Table 6-7. There were no differences between groups at completion with the exception of ISWT distance. Whilst both groups were similar at baseline, 'clinically strong' patients demonstrated greater distances walked at completion (365.0 (250.0-477.5)m vs. 200.0 (120.0-330.0)m, p=0.03), with significantly greater change from baseline to completion (265.0 (207.5-300.0)m vs. 120.0 (10.0-230.0), p=0.047). In addition, 'clinically strong' patients had higher SF-36 scores in the Physical Component Score (34.0 (282.2-41.4) vs. 29.4 (19.7-32.9), p=0.03) and Physical Function domain (40.0 (15.0-66.3) vs. 12.5 (5.0-27.5), p=0.005) at baseline although this difference between groups was not present at completion. Furthermore, 'clinically strong' patients, compared to those with ICU-AW performed better in terms of physical function as measured by the TUAG test at baseline (14.8 (13.1-18.5)s vs. 21.0 (16.0-36.0), p=0.04) although there were no differences between groups observed in the Barthel and STS-5 tests. No difference was evident between groups at completion or in change from baseline for any of these three measures of physical function.

Table 6-6 Comparison of baseline characteristics between patients with ICU-AW and 'clinically strong' patients

Characteristic	Trial Cohort (ICU-AW) (n=20)	Observational Cohort ('clinically strong') (n=21)	p
Age (years)	66.5 (54.5-73.3)	63.0 (49.5-70.0)	0.3
Gender (M:F)	6:14	16:5	0.005~
ICU diagnoses* (%)			
Medical	13 (65)	15 (71.4)	0.7~
Surgical	7 (35)	6 (28.6)	n/a
Chronic disease* (%)			
Respiratory	11 (55)	7 (33.3)	0.07~
Cardiac	9 (45)	7(33.3)	0.2~
Other#	8 (40)	10 (47.6)	0.8~
APACHE II	23.5 (20.3-29.5)	17.0 (12.5-19.5)	<0.0001
SOFA (ICU admission)	11.0 (8.0-13.5)	10.0 (7.5-12.0)	0.4
Duration MOF (days)	10.0 (6.0-12.8)	9.0 (3.5-14.5)	0.6
MV (days)	10.2 (6.8-14.0)	9.0 (4.3-20.4)	1.0
CPAP (days)	1.3 (0.2-5.0)	1.5 (0.4-2.6)	0.6
Tracheostomy (%)	8 (40)	8 (38.1)	-
ICU LOS (days)	13.5 (8.5-19.3)	10.0 (6.5-27.0)	0.9
CC LOS (days)	18.0 (11.5-31.8)	13.0 (10.0-37.0)	0.8
Ward LOS (days)	23.5 (10.3-43.0)	13.0 (6.5-19.5)	0.03
Hospital LOS (days)	46.0 (25.0-61.8)	30.0 (19.5-47.5)	0.2

Data are presented as median (interquartile range) or n (%). *ICU diagnosis and chronic disease indicates frequency of occurrence. Patients could present with more than one comorbidity. #Other chronic comorbidities included diabetes mellitus, osteoarthritis/gout, stable chronic renal disease. p values derived from Mann-Whitney test or Fisher's exact test~. Note one p-value applicable for contingency analysis of proportion of medical and surgical patients across both groups.

Abbreviations: ICU = intensive care unit. APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = Sequential Organ Failure Assessment. MOF = multi-organ failure. MV = mechanical ventilation. CPAP = continuous positive airway pressure. LOS = length of stay. CC = critical care. ICU-AW = intensive care unit-acquired weakness. MRC-SS = Medical Research Council Sum-Score.

Table 6-7 Comparison of outcome measures between patients with ICU-AW and 'clinically strong' patients

Characteristic	Trial cohort (ICU-AW) (n=16)	Observational Cohort ('clinically strong') (n=14)	p
ISWT (m)			
baseline	40 (10.0-80.0)	80.0 (30.0-212.5)	0.1
completion	200.0 (120.0-330.0)	365.0 (250.0-477.5)	0.03
change	120.0 (10.0-230.0)	265.0 (207.5-300.0)	0.047
6MWT (m)			
baseline	160.0 (110.5-221.0)	167.0 (60.0-293.5)	0.8
completion	330.0 (240.0-422.5)	433.5 (318.3-481.0)	0.1
change	160.0 (36.5-208.5)	157.5 (131.3-321.3)	0.5
SF-36 PCS (/100)			
baseline	29.4 (19.7-32.9)	34.0 (28.2-41.4)	0.03
completion	34.6 (46.5-55.1)	42.7 (35.7-48.5)	0.2
change	6.3 (-3.2-16.2)	6.4 (1.7-13.1)	0.9
SF-36 PF (/100)			
baseline	12.5 (5.0-27.5)	40.0 (15.0-66.3)	0.005
completion	40.0 (20.0-73.8)	70.0 (41.8-80.0)	0.1
change	20.0 (0.0-60.0)	23.5 (3.8-31.3)	0.8
Barthel (/100)			
baseline	87.5 (75.0-95.0)	97.5 (85.0-100.0)	0.08
completion	100.0 (86.3-100.0)	100.0 (98.8-100.0)	0.5
change	10.0 (1.3-23.8)	0.0 (0.0-15.0)	0.2
TUAG (s)			
baseline	21.0 (16.0-36.0)	14.8 (13.1-18.5)	0.04
completion	10.0 (8.0-19.0)	8.0 (6.8-10.0)	0.06
change	-7.0 (-24.0—2.0)	-6.0 (-9.3--3.8)	0.6
STS-5 (s)			
baseline	22.5 (16.8-29.5)	19.0 (10.8-26.0)	0.3
completion	16.0 (11.5-20.0)	11.4 (8.9-17.5)	0.2
change	-3.8 (-15.0-1.9)	-3.5 (-11.0--0.5)	0.98

Data are presented as median (interquartile range). p values derived from Mann Whitney test analysis. n=14 for TUAG and STS-5 for the randomised cohort.

Abbreviations: ISWT = Incremental Shuttle Walk Test. 6MWT = Six Minute Walk Test. SF-36 PCS = Short Form-36 Physical Component Score. SF-36 PF = Short Form-36 Physical Function domain. TUAG = Timed Up and Go. STS-5 = Sit to Stand 5 times.

6.3.4 Effect of diagnosis of ICU-AW on physical performance at early study milestone points

Patients were recruited into both the interventional trial and observational cohort study at ICU discharge according to MRC-SS. Follow-up of patients and delivery of the EBRP commenced at hospital discharge, termed baseline. As previously

detailed, patients in the trial cohort had improved MRC-SS by hospital discharge with an absence of ICU-AW by this time-point (Chapter 6.3.1.1). To investigate the influence of ICU-AW diagnosis on physical performance between these two study milestones, results of exercise capacity (ISWT and 6MWT) and physical function (Barthel scale, TUAG and STS-5) were analysed according to MRC-SS.

6.3.4.1 ICU discharge

At ICU discharge, only measures of MRC-SS and physical function were examined. Assessment of exercise capacity was not considered clinically appropriate in patients at this time-point.

18 patients with ICU-AW (MRC-SS <48/60) from the trial cohort (Figure 6-2) and 20 patients 'clinically strong' patients without ICU-AW (MRC-SS ≥48/60) from the observational cohort (Figure 6-3) had physical function data at ICU discharge. All patients, with the exception of missing data for one with ICU-AW, had Barthel scores and SF-36 PF scores.

There was a difference in Barthel score between those patients with and without ICU-AW (20.0 (15.0-22.5) vs. 62.5 (40.0-78.8), $p<0.0001$). With data combination from both groups, MRC-SS demonstrated a direct relationship with Barthel score ($r=0.8$, $p<0.0001$). a similar relationship was observed between MRC-SS and SF-36 PF domain ($r=0.8$, $p<0.0001$). 'Clinically strong' patients demonstrated greater SF-36 PF domain scores than patients with ICU-AW (15.0 (5.0-55.0) vs. 0.0 (0.0-5.0), $p=0.0007$). When the data from both groups were combined, MRC-SS showed a direct correlation with SF-36 PF domain ($r=0.6$, $p<0.0001$).

In the ICU-AW patient cohort, TUAG and STS-5 were not possible in one patient due a rapid discharge process and 2 patients unavailable for testing. A further 13 patients were either unable to perform the testing when attempted (n=5), or testing was not considered clinically appropriate due to mobility status (n=8). In the cohort of 'clinically strong' patients, 4 patients were unable to perform both TUAG and STS-5 when attempted. None of the patients were deemed unable to undergo physical functional assessment. This ability to complete measures of

physical function differed between patients with and without ICU-AW (unable to perform/able to perform, 13/2 vs. 4/16, Fisher's exact test, p=0.001). Due to limited data for TUAG and STS-5 for the ICU-AW group, analysis of differences in scores between groups was judged not to be statistically useful. Overall, when data from the groups were combined, MRC-SS demonstrated a negative relationship with STS-5 (r=-0.6, p=0.009) and TUAG (r=-0.5, p=0.047).

6.3.4.2 Hospital discharge

At hospital discharge 17 patients from the trial cohort were able to undergo assessment (Figure 6-2) and 19 patients from the observational cohort study (Figure 6-3). All patients completed the Barthel test and SF-36 PF domain scores. Data were unavailable from 3 patients from the trial cohort for TUAG and STS-5 (as previously reported, for one patient due to rapid hospital discharge, and missing data for 2 further patients). All patients completed ISWT and 6MWT. There was no patient unable to perform measures on attempt, nor did clinical status i.e. mobility levels, preclude testing in any patients. Statistical analysis of differences between groups for ability to perform measures was not appropriate as numbers were too small. When the groups were combined, MRC-SS observed to correlate with Barthel score (r=0.6, p=0.0002), TUAG (r=-0.5, p=0.007), STS-5 (r=-0.4, p=0.01), SF-36 PF domain (r=0.4, p=0.009) and ISWT (r=0.5, p=0.004). There was no relationship observed between MRC-SS and 6MWT (r=0.3, p=0.08). The comparison between study groups for physical function and exercise capacity measures is reported previously in Table 6-7. Interestingly no patient from either the trial or observational cohort study, demonstrated ICU-AW according to handgrip dynamometry thresholds (11kg for males, 7kg for females [36]) at either baseline or completion.

6.3.5 Eligibility criteria into the randomised controlled trial and discharge outcomes of excluded patients

Eligibility criteria applied to patient enrolment into the current interventional trial were determined based upon clinical, pragmatic and logistical rationale. However this resulted in a large number of patients who were excluded due to failure to

meet relevant entry criteria (Figure 6-2, Table 6-1). To determine if these eligibility criteria were different from previous studies, a comparison was made with inclusion and exclusion criteria reported from similar interventional trials (Table 6-9). Consistency was demonstrated across all studies.

To gain insight and understanding of the potential ongoing rehabilitation requirements following hospital discharge of the excluded cohort, hospital discharge status and outcomes for these 743 patients documented on hospital electronic databases were reviewed (Table 6-8). Almost 40% (292/743) of patients demonstrated a level of mobility sufficient for discharge home, albeit it is not known whether this represented a return to their premorbid levels of physical functional ability. 24.4% (181/243) of patients required ongoing rehabilitation input delivered either in a residential setting or by domiciliary services. Whilst not specified, current practice at both study sites would suggest that these were generic rather than specific post-ICU services. The community discharge destination of repatriated patients was unknown. It is possible, and likely, that a proportion of these patients may also have required ongoing rehabilitation input.

Table 6-8 Hospital discharge outcomes for patients excluded from the randomised controlled trial

Hospital discharge outcome	n (%)
Home; documented return to pre-morbid level of mobility safe for discharge	292 (39.3)
Death	181 (24.4)
Not known	76 (10.2)
Discharged to rehabilitation setting	72 (9.7)
Home; ongoing rehabilitation needs	66 (8.9)
Repatriation to referring institution*	56 (7.5)

n=743. *community discharge destination and ongoing rehabilitation needs unknown

Table 6-9 Eligibility criteria of post hospital discharge rehabilitation studies

Study	Inclusion Criteria	Exclusion Criteria
Batterham *et al* [179, 195]	Age between 18 and 65yrs; traumatic or primary sepsis event; emergency ICU admission; mechanical ventilation ≥3days; discharged home within 6m of admission; not currently involved in a rehabilitation programme; able to climb a flight of stairs unaided	Hospitalised >6m post ICU admission; enrolment in exercise or rehabilitation programme; inability to complete initial CPET; contraindication to CPET procedure; moderate to severe heart failure; moderate or above aortic stenosis; hypertrophic cardiomyopathy; symptomatic arrhythmias; severe disability; spinal cord injury; primary muscular disorder; uncontrolled epilepsy; pregnancy; BMI >40
Denehy *et al* [177, 196]	Resident within access to hospital; no neurological, spinal or musculoskeletal dysfunction preventing participation in physical rehabilitation; ICU length of stay ≥5days; age ≥18years; English-speaking and understanding	Major CNS disorders resulting in permanent weakness non-responsive to exercise; conditions rendering participation in exercise hazardous, such as unstable fractures; imminent death or planned palliative management within 48hrs; inability to perform study physical outcome measures pre-morbidly due to a condition impairing mobility
Jackson *et al* [183]	Age ≥18years; English-speaking and understanding	Cumulative ICU LOS >5days within previous 30days excluding current admission; severe cognitive or neurodegenerative disease preventing independent living at baseline; HBI; mental health issues; imminent death or planned palliation; resident beyond study site region; onset of causal ICU admission >72hrs pre-admission; cardiac bypass surgery within 3m; normal cognitive and physical function at hospital discharge; lack of telecommunication equipment to receive intervention
Elliott *et al* [180, 198]	Age ≥18years; ICU LOS ≥48hrs; mechanical ventilation ≥24hrs; discharged home to self-care or carer (non-institutionalised); resident with hospital geographical region to permit home visits	Neurological, spinal or skeletal dysfunction preventing participation in physical rehabilitation; palliative care; organised rehabilitation related to ongoing chronic disease management; insufficient cognitive function for completion of outcome measures
McWilliams *et al* [185]	Invasive mechanical ventilation ≥48hrs	Physical inability to undergo gym-based rehabilitation programme; terminally ill; mental impairment precluding cooperation with rehabilitation programme
Jones *et al* [178]	Admitted to ICU; received mechanical ventilation	ICU LOS <48hrs; burn injuries; inability to follow the interventional manual or language difficulties; neurosurgical diagnoses; pre-existing psychotic illness; discharged for terminal care and unlikely to survive 6m follow-up period

Cuthbertson *et al* [184, 199]	ICU admission at any point during hospital stay	Age <18yrs; not expected to survive to leave hospital; unable to complete questionnaires or attend clinics
O'Neill *et al* [192]	Age ≥18years; ICU admission requiring >96hrs mechanical ventilation; planned discharge to home (self-care/carer); willing and able to participate in exercise; medically fit to participate in intervention	Inability to participate due to neurological, spinal or skeletal dysfunction affecting ability to exercise; cognitive impairment affecting ability to understand the intervention or complete outcome measures; participation in another rehabilitation programme due to ongoing chronic disease; other medical contraindications to participation in an exercise programme
Battle *et al* [191]	Age ≥18years; ICU LOS >48hrs; discharged home and attending follow-up clinic within 6m of ICU discharge; capacity to follow instructions; not already enrolled in a rehabilitation programme; live within commutable distance to study site	Medical contraindications to exercise including unstable angina or myocardial infarction within preceding month, unmanaged valvular problems, patients awaiting further definitive treatment e.g. open abdominal wound, pregnancy where patient advised against exercise
Griffiths *et al* [190]	Age ≥45yrs; ICU LOS ≥5days	Physically not capable of engaging with the practical requirements of the study

Abbreviations: CNS = central nervous system. HBI = hypoxic brain injury. ICU = intensive care unit. LOS = length of stay. CPET = cardiopulmonary exercise test. BMI = body mass index.

6.3.6 Power calculations based on current data

Data from the current study were used to determine the power calculation for any potential future trial. Given the inconsistency in differences between the trial and observational study cohorts, these data were pooled. This resulted in a total of 30 patients, which meets suggested sample sizes for estimating outcome [289, 290]. Outcome measures of ISWT, 6MWT, SF-36 Physical Component Score and Physical Function domain were considered as these are commonly reported outcome measures used in similar studies. Often MCID values are used to define a difference between standard treatment and intervention groups in randomised trials, and the power calculation determined based on this expected difference. In the current study all patients demonstrated change over the three month follow-up period that exceeded known MCID data, albeit for chronic respiratory disease. A predicted difference of 20% between the standard treatment arm and intervention group was therefore used to undertake power calculations.

Based on a mean change in the current standard treatment group of 193 (130)m for the ISWT, and assuming a 20% difference with intervention, 184 patients in each group would be required at 80% power, and $p<0.05$. For the 6MWT this figure increases to 210 patients per group (current standard treatment arm mean change 171 (121)m).

Far greater sample sizes would be required to detect a potential 20% difference between standard treatment and intervention groups based on current data for the SF-36 PCS (current standard treatment arm mean change 7 (10)points) requiring 732 patients per group, and for the SF-36 PF domain, 446 patients per group (current standard treatment arm mean change 24 (26)points).

6.4 Discussion

This pilot randomised controlled trial investigating an exercise-based rehabilitation programme delivered following hospital discharge in survivors of critical illness with ICU-AW, demonstrated there was no beneficial effect across a range of clinical and

physiological outcomes. However the feasibility of the intervention was evident with a high completion rate, an absence of associated adverse events, and high patient-reported acceptability. Although 'clinically strong' patients, who were observed over the same three month period, demonstrated significant improvements in exercise capacity, health-related quality of life and physical function, a comparison between the trial cohort with ICU-AW and the observational cohort showed an inconsistent pattern in physiological, clinical and patient-centred outcomes. Patients with ICU-AW at ICU discharge, and who were eligible for trial enrolment, subsequently had an improvement in their MRC-SS by hospital discharge when the intervention commenced.

These data highlight the limited sensitivity of MRC-SS as a measure to base inclusion into a post critical illness rehabilitation programme following hospital discharge. Indeed, the timing of assessment for eligibility and enrolment needs to be contemporaneous with the treatment commencing. In addition, this pilot study highlighted a number of important methodological considerations in the design, conduct and evaluation of a future trial, not least with regard to eligibility criteria, as demonstrated by the high screening rates of patients failing to meet the inclusion or meeting the exclusion criteria. Furthermore, the timing, frequency and intensity of rehabilitation delivery require careful consideration as the 'dose' of rehabilitation needs to accelerate and enhance the natural recovery that was observed. Finally, in a future trial there must be close attention focussed on the selection of the most appropriate primary outcome to evaluate the effectiveness of the intervention, and the balance between clinically focussed objective and patient-centred subjective measures which impose differing burdens on the patient.

6.4.1 Clinical relevance of the findings in the context of previous data

In this RCT there were no differences observed between those patients receiving the exercise-based rehabilitation intervention and those receiving standard care at three months, albeit the trial was not powered for this purpose. A mixed pattern was observed in baseline, completion and degree of change values between groups with the change in ISWT and 6MWT being greater in the standard treatment group, but the

exercise-based rehabilitation group demonstrated greater improvement in SF-36 PF domain score and HADS score.

These findings are not dissimilar to previously reported data of post hospital discharge exercise-based rehabilitation programmes [177, 179, 180] but the current cohort had greater illness severity, longer duration of mechanical ventilation, and longer ICU and hospital admission compared to these studies. The intervention investigated by Batterham *et al* [179] comprised twice-weekly supervised exercise sessions using cycle ergometry to achieve target levels of perceived exertion, with encouragement to undertake one additional unsupervised session. Whilst a small benefit was observed in the intervention group for the primary outcome of anaerobic threshold in the short term (week 9) this was not sustained at the end of the trial (week 26). A suggested benefit to physical and mental health-related quality of life was also proposed but this was not substantively demonstrated on examination of the confidence intervals of results. Denehy *et al* [177] investigated a triple-phase intervention delivered in the ICU, following transfer to the ward, and post hospital discharge. Post hospital discharge, the intervention consisted of an eight-week, twice-weekly, outpatient, hospital-based exercise programme with cardiovascular, strength and functional content. There were no significant differences observed for the primary outcome, six minute walking distance, or other measures of physical performance or health-related quality of life at 12 months, albeit the rate of change of recovery was greater for the six minute walking distance in the intervention arm. Elliott *et al* [180] investigated a post hospital discharge intervention of an outpatient, home-based, semi-supervised programme of endurance and strength training, and reported that there were no differences between intervention and standard treatment groups at 8 and 26weeks follow-up.

Additional recent data have also reported improvements in physiological parameters of physical fitness including peak oxygen consumption and anaerobic threshold measured during cardiopulmonary exercise testing, as well as mental and physical health-related quality of life following exercise training programmes [182]. However not all changes were significant, and the data are currently only available in abstract form, limiting detailed comparison to the current study in this thesis. The clinical

utility of cardiopulmonary exercise testing, (CPET), as an outcome measure in such trials is useful in terms of understanding the physiological effect of rehabilitation in this patient group, but is lacks detail on clinical and cost effectiveness. Whilst previous data have reported safety and feasibility of CPET in survivors of critical illness [291], such testing is costly, time-consuming, and limited to institutions with the necessary equipment, expertise and personnel for conduct and interpretation. As such it may have limited wider uptake, but could serve to validate results of field walking tests which represent a more pragmatic approach to assessment of exercise capacity in this population [53].

Only one randomised controlled trial to date reports significant improvement in six minute walking distance and balance in patients receiving a six-week supervised exercise programme, with improvements in anxiety and depression, and grip strength [181]. Again, these early results from a small sample, whilst promising, are available in abstract form only with, as expected limited detail provided of the intervention, and therefore comparison with other trial interventions is not possible. In the past, rehabilitation manuals guiding self-directed exercise have been shown to improve physical function [178], although it is difficult to ascertain from this type of intervention and delivery, the exact nature and intensity of exercise prescription.

The current trial is novel as it required all patients to have a diagnosis of ICU-AW at ICU discharge as a specific inclusion criterion. Indeed, given the previous published data that reported the association between ICU-AW and prolonged ventilation, ICU and hospital length of stay, and ongoing physical functional impairment [11, 30, 36, 37, 105, 106, 292], incorporating the diagnosis of ICU-AW as an inclusion criterion was considered appropriate. Based on previous evidence, it was hypothesised that these patients demonstrating peripheral skeletal muscle weakness on discharge from the ICU would have ongoing impairment of physical function and a rehabilitation intervention would accelerate and enhance recovery.

However, these data, combined with the data from *Chapter 3*, have shown that manual muscle testing using the MRC-SS test and a score less than 48 out of 60 as a diagnosis of ICU-AW lacks sensitivity and specificity to predict clinical outcome. Specifically, in

the current trial, MRC-SS test added limited clinical utility to categorise patients with ICU-AW to define the most appropriate target group for exercise-based rehabilitation intervention. When compared to the observational cohort of 'clinically strong' patients with MRC-SS greater than 48, patients who demonstrated ICU-AW at ICU discharge were similar for all baseline characteristics with the exception of gender, illness severity at ICU admission and ICU length of stay. The gender difference is interesting as it would be expected that men would be stronger than women in the pre-morbid state prior to ICU admission and this again highlights a further caveat in the MRC-SS approach. This is also paradoxically supported by the association between MRC-SS and physical function. These correlations were driven by the MRC-SS values from 'clinically strong' patients as there were limited physical function data from patients with ICU-AW.

Interestingly by hospital discharge and start of the follow-up period patients who had previously presented with a clinical diagnosis of ICU-AW at ICU discharge, all had MRC-SS greater than 48 out of 60 and would have re-categorised as 'clinically strong'. This demonstrates the ceiling effect limitation of MRC-SS testing. One would argue that all patients, both in the trial and observational cohort study, were similar in terms of peripheral skeletal muscle strength, albeit the gender and severity of critical illness had affected the trajectory of recovery. Patients with the greatest skeletal muscle weakness at ICU discharge, who were indeed the sickest patients at ICU admission were likely to have undergone greater muscle wasting during their ICU admission as previously demonstrated by our group [250]. Hence it would be postulated that their ward stay was protracted whilst they received more intense rehabilitation interventions than those without ICU-AW in order to achieve a level of function sufficient for hospital discharge, at which point the MRC-SS was not able to distinguish between groups. These data were not formally captured in the current study but any future trial must collect the type, frequency and intensity of ward-based rehabilitation.

Denehy *et al* [177] are the only other investigators to report prevalence of ICU-AW, based on MRC-SS testing. At enrolment, within ICU, levels were at approximately 20% across control and intervention arms. Whilst not specifically re-evaluated at the start

of their post hospital discharge intervention, given the initial relatively low percentages of patients it is highly possible for the proportion of patients with ICU-AW to have reduced further, and for the cohort at this stage to have been 'clinically strong'. The value of the MRC-SS to characterise survivors of critical illness in the context of delivering rehabilitation interventions appears therefore limited.

Both the trial and observational study cohorts demonstrated improvements above the reported MCID values for exercise capacity and subjective physical function scores (ISWT, 6MWT and SF-36 PF domain), albeit specific MCID data for the post critical illness population have yet to be established. Although application of the MCID can be conceptually problematic [293], consideration of these values permits clinical interpretation rather than basing conclusions solely on statistical analyses [177]. Natural recovery in the patient groups from the trial and observational cohort study was above the MCID of an intervention, which is an important observation as any future rehabilitation intervention will be required to accelerate and enhance the natural history of recovery following critical illness. We need to consider whether rehabilitation should be withheld for the first 3 months at a time when the trajectory of recovery, with the addition of standard treatment, is satisfactory. This would reduce the clinical and physical burden on the patient at a time when they are recovering in the community, supported by family networks, outside the hospital. This approach of delayed rehabilitation until natural recovery reaches a plateau must be balanced against the observation that the exercise capacity achieved, in terms of six minute walking distance, across all patients was lower than predicted values [288].

6.4.2 Critique of the method

The current trial was intended as a pilot feasibility process to investigate an exercise-based rehabilitation programme for post critical illness patients with ICU-AW, delivered following hospital discharge. The evaluation of this process offered valuable insight into the methodological considerations which would be important in the development of a future trial. Specifically, it provided data to guide defining the target population as well as the timing and type of rehabilitation intervention. These current data, as discussed in *Chapter 6.4.1,* must be interpreted with caution as the trial was

not powered to detect a difference in any outcome measure. A small sample size, requiring non-parametric analyses restricted to limited inferential testing, denied definitive conclusions about the effect of rehabilitation to be drawn.

Due to complexity of both the intervention under investigation, exercise-based rehabilitation, and the target patient population, survivors of critical illness, process evaluation represents a useful approach for distinguishing failure of the intervention to cause an effect, which reflects the underlying concept or theory, from failure of the implementation of an effective intervention delivery [294, 295]. Process evaluation accounts for the multifaceted nature of trials of complex interventions, where there are often several interacting components [296], to understand underlying mechanisms relating to context, setting and relevant stakeholders which can influence outcome [297], and this is embedded in recent Medical Research Council (MRC) guidance on the development, evaluation and reporting of complex interventions [298]. Whilst ideally a prospective and systematic process evaluation would form an allied component of such an RCT [294, 295, 297], in this instance it has been considered retrospectively to facilitate review of the pilot process.

The following discussion adopts a relevant model used in a recent editorial by Salisbury and Walsh [299] to accompany a systematic review of rehabilitation interventions for patients within the ICU, namely that of the "PICO" principle (Population, Intervention, Control, Outcome) which is the cornerstone for development of well-built clinical questions [300]. More recently, this concept has been expanded to include review of the current evidence pertaining to the subject of interest, and also appropriate study type [301].

6.4.2.1 Evidence on the subject

The current evidence, or relative lack thereof, regarding rehabilitation interventions for post critical illness patients following hospital discharge has been reviewed in detail in *Chapter One*, Introduction, and previously published by the researcher (BC) [186]. Whilst not systematic in design as suggested by the MRC Framework [298], the integrative nature of this narrative review allowed for inclusion of varied sources of

evidence, including study protocols, to further inform the limited knowledge-base. At the time of designing the current study, minimal data existed to guide the content of exercise-based rehabilitation for this patient population, albeit national guidelines advocated their implementation [136] and there was a growing research interest in the field. Instead, development of the intervention was directed by the data and international guidelines detailing the effectiveness of pulmonary rehabilitation programmes for patients with chronic respiratory disease, including from the researcher's own group [187, 188, 204, 286, 287, 302].

6.4.2.2 Target population

Critically ill patients are a challenging population for rehabilitation research at any stage of their recovery pathway. Marked heterogeneity arising from a multitude of causal diagnoses for ICU admission, wide-ranging illness severity from single- to multi-organ failure, chronic comorbidity and trajectory of illness progression mean that patterns of response to interventions will inherently vary between individual patients, even if eligibility criteria have been applied in an attempt to achieve a more 'homogenous' cohort included in a trial.

In the current study, eligibility criteria included a range of clinical, pragmatic and logistical factors. During the course of the pilot study, when recruitment was identified as slower than anticipated, these were compared to those used in similar studies and consensus appeared evident. Nonetheless application of these criteria resulted in an extremely high ratio of excluded to included patients. Denehy *et al* [177], Elliott *et al* [180] and Batterham *et al* [179] similarly experienced this, with recruitment levels of 150 patients out of 764 screened, 195 patients from 5980 screened, and 59 patients from 740 screened respectively, and two trials failing to reached *a priori* calculated sample sizes [177, 180].

Assuming existing eligibility criteria for post hospital discharge rehabilitation trials are maintained, the time-frame required to recruit sufficient patient numbers for a larger-scale trial necessitates consideration. Clearly multi-centre trials would facilitate speed of recruitment, but involvement of both district general hospitals as

well as specialist centres would also contribute to enhancing enrolment, as evidenced by the difficulties encountered in recruitment in the current study attributable to the tertiary referral status of both organisations.

Defining the patient population most likely to benefit from post hospital discharge rehabilitation requires better understanding [132]. Experience from the current study, which specifically included patients with ICU-AW diagnosed using the MRC-SS cut-off of less than 48 out of 60 suggests that this approach is less useful given the inconsistent differences between these patients and 'clinically strong' patients, and lack of rigour of the MRC-SS tool itself [57]. Clinically-relevant peripheral skeletal muscle weakness may better be characterised by functional outcomes which could form eligibility criteria or be used to stratify groups. Furthermore, screening and randomisation may be better conducted at the point at which an intervention is scheduled to commence. Failing this, studies need to accurately capture and record interim treatments that may influence recovery and outcome of patients. Hence, in the current trial, randomisation may have been more appropriate occurring at hospital discharge prior to the start of the rehabilitation programme, especially as standard ward-based input to trial patients following recruitment at ICU discharge was not formally recorded.

6.4.2.3 Intervention

Dictionary definitions of rehabilitation define a process of restoring an individual to health or normal life [303]. In the context of recovery following critical illness, residual impairments range across physical, psychological, cognitive and functional domains which is now reported by some as the 'post intensive care syndrome' [125]. A comprehensive rehabilitation programme must encompass strategies addressing each of these facets, demonstrate a flexible, adaptable approach to meet the individual needs of patients, and furthermore consider the impact and burden placed on family and care-givers [123, 124]. The current trial focussed on an exercise-based intervention primarily to manage physical deficits in patients. However failure to address other 'morbidities of critical illness' [132] may have contributed to the results. In the future multidisciplinary and multimodal rehabilitation programmes

may elicit greatest response through the synergistic effect of optimising one element of impairment on another e.g. the benefit observed in physical performance as a result of improved mental health, and vice versa. The *Enhanced Recovery After Surgery* pathway offers one approach that critical illness rehabilitation programmes could model incorporating evidence-based 'care bundles' of practices [304].

Variability currently exists with regard to structure, content, format of delivery, intensity, frequency and timing of exercise prescription amongst current published trials and available protocols, and to date there has been no optimum level established. This lack of consistency challenges synthesis of data and implementation of research findings into clinical practice. The current trial attempted to describe the intervention with as much detail as possible, in keeping with recommendations for nonpharmacological trials [305].

The current trial adopted an outpatient, hospital-based style of intervention which may be an important option for managing frailer, more dependent patients who require closer supervision whilst undertaking exercise. However, this more 'traditional' method of intervention delivery may not be ideal for engaging all potential patients, and in the future use of alternative technologies such as mobile phone and tablet applications, websites and interactive patient forums may offer more appealing options. Nonetheless the current trial achieved a high completion rate, although this could be attributable to provision of transport to attend sessions, which may otherwise have precluded patients from travelling to the hospital. Clinical factors were responsible for the majority of non-attendances, which may also affect adherence to rehabilitation delivered via other formats.

A combination of cardiovascular, upper and lower limb strength, balance and functional exercises were included in sessions, and tailored to meet each patient's ability. Initial exercise prescription was based on objective outcome measures and re-evaluated during the course of the programme. Furthermore patients exercised for nearly all of the available time during each session. Despite this, within each session exercise intensity was determined using the subjective Borg scale of perceived exertion, although target levels were set aiming for moderate to severe exertion.

Patients may not have exercised at levels sufficient to elicit physiological benefit through reluctance or anxiety regarding undertaking exercise, or over-exertion, and the intervention may have been too conservative. The former scenario requires emphasis on patient education regarding safe levels of exercise, the latter a close attention to individual exercise prescription. The contrast between the relatively high attendance rates for the intervention versus the potential for suboptimal exercise intensity suggests lack of intervention effectiveness rather than implementation although this is difficult to confirm given the small size of the cohort. Cardiopulmonary exercise testing could have a role in determining if patients are exercising at an intensity sufficient to evoke a physiological training effect.

Adopting a pragmatic approach and delivering the exercise-based rehabilitation intervention in parallel with existing pulmonary rehabilitation programmes, permitted patients to attend education sessions offered, although these varied in relevance as they were primarily targeted towards patients with chronic respiratory disease. This was a theme echoed within the acceptability feedback. Individual advice or education was available from the researcher (BC), but the *ad hoc* nature of this limited formal quantification or analysis. A recent review of studies involving delivery of education to post critical illness at the post hospital stage identified that few adhere to the content advised by NICE CG83, and that there were limited outcome measures available to evaluate education provision [306].

6.4.2.4 Standard treatment group

Accurate description of the standard treatment (control) arm involved in a trial of a complex intervention is important for greater interpretation and generalisability of results [307, 308]. Methods such as benchmarking or point prevalence studies to detail and evaluate existing levels of care or practice have recently been reported, particularly in reference to exercise rehabilitation standards within the ICU [309-311]. Standardised reporting of usual practice and the context and processes of care typically in operation, has a number of benefits including improving safety monitoring, facilitating translation of findings into local context, and enhancing understanding of the differences between groups with regard to intensity of

interventions received [312, 313]. This latter point is exemplified by the findings of Denehy *et al* [177] at the 'in ICU' stage of their tripartite intervention when considering previous literature on early mobilisation within the ICU. Usual care for their ICU patients was reflected by 52% of patients receiving active mobilisation including sitting out of bed or marching on the spot [155], in excess of the *intervention* arm delivered by other authors [163, 164, 285] although international differences in physiotherapy practice are acknowledged to be a contributory factor to this [177]. That the host institution in Denehy *et al's* study was also reported as demonstrating usual care over and above that across other Australian ICUs [309] further highlights this point. Undertaking a benchmarking exercise would be valuable by all organisations participating in any multi-centre study involving delivery of a rehabilitation intervention to ascertain a common level of' 'standard treatment' practice and to ensure that results were not influenced by variation of practice at an organisational level.

In the current study, usual care post hospital discharge within the study involved the standard treatment arm receiving a weekly telephone call from the researcher. This was not detailed in the original protocol, but was strongly advised by the ethical review board as a means of ensuring all study participants were monitored during the study period. Whilst no specific advice regarding exercise rehabilitation was provided during these phone-calls, this does represent enhanced post ICU input than these patients would normally receive. Furthermore standard treatment arm patients could also be discharged from hospital in receipt of generic rehabilitation services such as intermediate care or community therapy at the discretion of the clinical team. All standard treatment patients in the current trial were discharged to their home environment, however lack of formal evaluation of additional services received by these patients represents a weakness of the current protocol as these interventions could have contributed to expediting recovery and therefore influenced results.

6.4.2.5 Outcome

A range of different instruments for measuring physical functional performance have been used in survivors of critical illness, although sensitivity, specificity,

reproducibility and clinical utility of these tools has yet to be ascertained [53]. As such appropriate outcome measures for evaluation of rehabilitation interventions remain to be determined [132]. Outcome measures must be sensitive to change over time and the relative 'floor' and 'ceiling' effects must be considered. For example in the current study, a number of patients in both the trial and observational study groups demonstrated high Barthel scores at baseline indicating that this clinical tool has limited usefulness to track the trajectory of recovery. The World Health Organisation International Classification of Functioning, Disability and Health outlines a multi-dimensional framework that can guide outcome measure at an individual, institutional and social level, considering domains of structure, activity and participation [314].

In this way a 'package' of outcome measures may be required to best reflect response to interventions, flexible to address the range of impairments evident across the continuum of recovery [177]. However implementing such a battery of assessment measures may be difficult to achieve in research and clinical practice. The current trial utilised a range of outcomes including exercise capacity, health-related quality of life, peripheral muscle mass and strength, and physical function. All these outcomes varied in the amount of "effort" required from patients for performance. This extensive investigation was challenging to complete by this post critical illness patient cohort and contributed to missing data. When considered individually, each outcome measure may not appear time-consuming but the cumulative effect resulted in a burden of assessment to patients, which may have influenced the quality of their performance and willingness for ongoing participation (Figure 6-4). Consideration is required for the logistical practicalities of acquiring such a volume of data in often frail patients with existing clinical consultations and investigations. In addition experience in the current trial observed that testing at hospital discharge could be influenced by patient availability on the ward, and changes to discharge planning at short notice. At completion, appointments were often coordinated with other hospital attendances to minimise patient inconvenience, but this imposed time constraints on data acquisition. Future consensus from a range of clinical and patient stakeholders for sets of core outcomes to evaluate effectiveness of rehabilitation interventions in trials will guide protocol development [315].

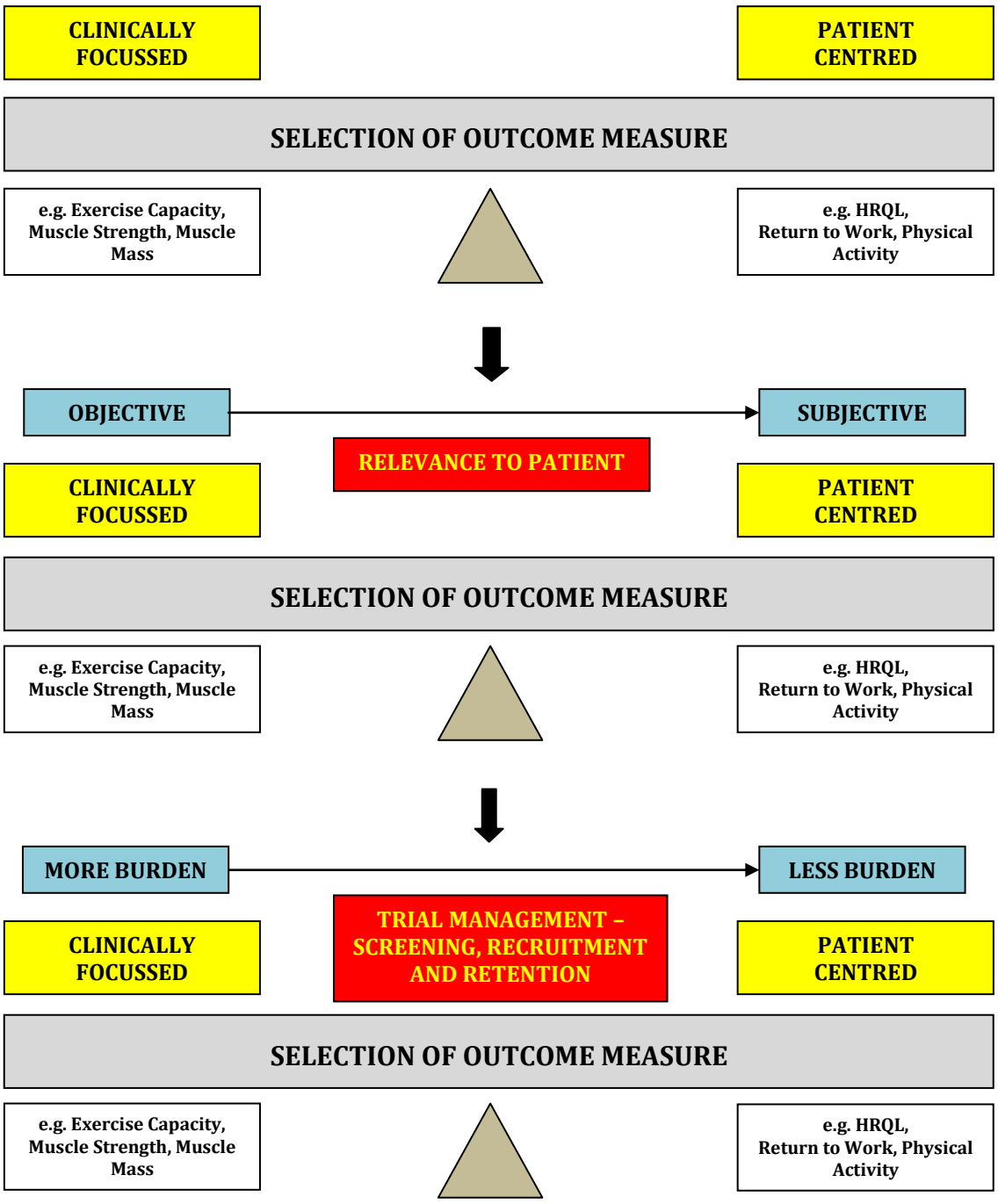


Figure 6-4 Schematic outline of outcome measure selection in trial management

Using exercise capacity, muscle strength, muscle mass, health-related quality of life, return to work and physical activity as examples. This outline demonstrates the balance between 'clinically focussed' and 'patient-centred' outcomes in terms of considering outcome measure selection on burden to patients and trial management.

Abbreviations: HRQL = health-related quality of life

6.4.2.6 Study design

The terms pilot study and feasibility study are often used synonymously in the literature. Essentially these processes can be considered 'test-runs' for some of the key components of the main trial to be conducted, answering the question 'Can this study be done?' [290, 316-319]. A thorough piloting stage is recommended in the development of complex interventions [298]. Randomisation is not an essential component of a pilot, feasibility study, even if the main trial in preparation will have a randomised controlled design [320]. Nonetheless some authors use the term 'pilot trial' where a randomised element is included [317, 321] although the lack of consensus for definitions of study types means that this is not widely adhered to.

As a pilot study, the current trial allowed testing of eligibility criteria to determine recruitment and retention rates, acquisition of data on a range of outcome measures, and implementation of the intervention on a small, albeit varied, cohort of patients, in keeping with the aforementioned purpose of a pilot feasibility study. In addition randomising patients provided valuable insight regarding the extent of natural, independent recovery of control patients, to further inform development of future interventions. The current study included 20 patients and 21 patients in the randomised trial and observational cohort study respectively. These are considered acceptable numbers for estimation of outcome measures and sample size calculations [289, 290]. Indeed these are within the range recently reported in a systematic review of UK Clinical Research Network-registered pilot and feasibility studies [322], albeit both randomised and observational groups experienced lack of completion. Variability in outcomes, with often large standard deviations, resulted in a range of estimated sample size estimates. With emerging data from other RCTs, a more sensible approach would be to base power calculations on pooled findings from across these trials to achieve greater robustness.

The current pilot study could be criticised for limited patient involvement in the design of the trial. Whilst acceptability feedback was acquired from patients receiving the intervention following completion, it is acknowledged that greater levels of input throughout the process would have offered further insight and informed decisions

regarding conduct of the study [298]. Furthermore, only a single researcher (BC) was involved in the conduct of all aspects of the pilot study for pragmatic reasons. Whilst potential researcher bias was essentially equal across all groups, this is a methodological limitation.

6.4.3 Future considerations

This study successfully met a number of intended feasibility outcomes namely to determine recruitment rate (numbers of patients screened vs. number eligible to participate and consenting to enrolment), the logistics of delivering the intervention and practical factors for consideration, compliance with the protocol in particular the exercise-based rehabilitation programme and patient acceptability of the intervention, and evaluation of potentially valuable outcome measures. Experience gained from this pilot trial could be of value in the future when designing, implementing and evaluating a larger-scale trial.

We observed a natural improvement in MRC-SS from the point of randomisation (at which point eligible patients were required to demonstrate ICU-AW as reflected by an MRC-SS <48/60) to the start of the intervention (at hospital discharge, by which stage the cohort no longer demonstrated ICU-AW). Whilst this signals that the MRC-SS may not be a sensitive tool to stratify patients for ongoing physical rehabilitation input, supported by observational data from a cohort of patients who never demonstrated ICU-AW, this would also highlight that in future trials, timing of randomisation must be contemporaneous with intervention commencement. Where this is not possible, detailed characterisation of clinical management received by patients in the interim period must be documented in order to ascertain the influence of this on patient performance.

We included a range of clinical, physiological and patient-reported outcomes, and whilst not formally measured, it is highly likely this introduced an element of outcome measure burden or fatigue. Certainly on a practical note, it was difficult to complete all measures at all time points due to additional constraints on patient time and availability. Future consensus on the most appropriate outcome measures for

evaluation in rehabilitation trials for survivors of critical illness will facilitate selection of outcomes in trials. Ideally a core outcome measure set would include measures representing domains of activity, restriction and participation as reflected by the World Health Organisation model [323].

6.5 Conclusion

In this pilot feasibility study of exercise-based rehabilitation following hospital discharge for survivors of critical illness with ICU-AW outcomes measured at three months, including exercise capacity, peripheral skeletal muscle mass, health-related quality of life and physical function, were not different between standard treatment and exercise-based rehabilitation intervention groups. Furthermore, differences between randomised patients, and an observational cohort of 'clinically strong' patients revealed inconsistent differences. In addition, the use of a diagnosis of ICU-AW based on the MRC-SS cut-off of less than 48 out of 60, conferred limited clinical usefulness in identifying patients with ongoing rehabilitation requirements and who may respond to rehabilitation treatment post hospital discharge. Evaluation of the process highlighted methodological factors for further consideration. Notably, a consensus on eligibility criteria would be beneficial to optimise recruitment rates, and these may be further influenced by potential for delivery of the intervention in different formats. An emphasis on physical functional performance at the time of intervention delivery, in addition to the clinical factors related to the ICU admission may be warranted. Certainly this would enable a patient-focussed approach to trial enrolment. Furthermore, engaging patient stakeholders in all aspects of trial design would strengthen a future protocol. The variation in natural recovery observed in patients in the current study highlights the need to track the trajectory of recovery in this patient population to permit the timely implementation of interventions when a plateau of improvement is reached, which may vary widely between individual patients. This approach may therefore facilitate determining the optimum 'dose' of exercise prescription required for clinical effectiveness. The establishment of a consensus on core outcomes for use in future trials of complex interventions will also assist evaluation of the clinical and cost benefits of rehabilitation treatment.

Chapter 7 Implementation of NICE CG83 Clinical Guidance Following Hospital Discharge: a UK Survey of Rehabilitation Following Critical Illness

7.1 Introduction

The catastrophic and often long-term consequences of critical illness for survivors are well documented. Physical and psychological impairments, including reduced exercise capacity and health-related quality of life are known to persist for up to 5 years post index admission [103-105, 111, 324]. These features are now referred to as the 'post intensive care syndrome' [125]. In recent years the importance of survivorship, or the *quality* of survival, has been increasingly recognised [131], and the role of rehabilitation interventions to facilitate the recovery pathway for these patients has become a major focus for both clinicians and researchers [325].

In the UK, the National Institute of Health and Care Excellence (NICE) in 2009 published clinical guideline 83 (CG83) focussed on 'Rehabilitation after Critical Illness' [136] (available at http://publications.nice.org.uk/rehabilitation-after-critical-illness-cg83). This guideline profiled the importance of this area of clinical practice aiming to improve the standards of care and previously unmet clinical needs of this patient group. NICE CG83 advocated a continuum of multidisciplinary rehabilitation along the recovery pathway from within the ICU, following transfer to the ward, and beyond hospital discharge. Specifically at the point of hospital discharge it was recommended that patients were referred to appropriate rehabilitation services if ongoing needs were identified. At 2-3 months following hospital discharge, a review and functional reassessment of the patient were advised to determine the extent of recovery and additional rehabilitation input in the event of a slower than anticipated recovery or identification of new physical and/or psychological morbidity

However despite the intentions, widespread clinical implementation of these guidelines has been challenged by the limited evidence underpinning recommendations, and minimal detail provided to characterise optimum type, intensity, frequency and duration of exercise therapy and rehabilitations interventions [186]. In particular following hospital discharge survivors of critical illness can experience inadequate and poorly coordinated multidisciplinary care with inconsistent service provision which can be strongly influenced by local resources and geographical location [120].

Failure to implement national guidelines or respond to published evidence is not uncommon. Disparity between the prevalence of conditions such as chronic cardiorespiratory disease, diabetes mellitus and sleep=related disorders, and availability of recommended services for their management, is evident across the UK [326-328]. Previous surveys relating to critical care rehabilitation provision have focussed on ICU follow-up clinics [329] or physiotherapy practice within the ICU [330-337]. Two recent surveys have reported on NICE CG83 implementation but these were limited in volume and content, particularly at the post hospital discharge stage of the patient pathway, and restricted in geographical distribution [200, 201].

7.1.1 Aims of study

The aims of this study focussed on the implementation of NICE CG83 across the UK and rehabilitation practice at the post hospital discharge stage of the patient pathway:

1. To determine current UK prevalence of post hospital discharge follow-up for critical illness patients
2. To determine availability of post hospital discharge rehabilitation programmes for post critical illness patients, including structure, format, content and evaluation
3. To investigate barriers influencing provision of rehabilitation services, and use of alternative rehabilitation streams for post critical illness patients

7.2 Method

7.2.1 United Kingdom Intensive and Critical Care Units

Details for all adult ICUs across the UK (England, Wales, Scotland and Northern Ireland) were obtained via direct communication with the Intensive Care National Audit and Research Centre (ICNARC) and the Scottish Intensive Care Society Audit Group (SICSAG). Details of organisations in which these units were based were recorded in an Excel spreadsheet. Organisations with general ICUs were identified for

inclusion, and totalled 240 organisations (85 university teaching (UT) and 155 district general (DG) hospitals) of which 193 were based in England, 23 in Scotland, 15 in Wales and 9 in Northern Ireland. Specialist ICUs e.g. neurosciences, cardiothoracic surgery or cancer were excluded. For the purposes of the current study, where institutions were listed in duplicate on the original ICNARC or SICSAG database for multiple critical care units (e.g. both Intensive Care Unit and High Dependency Unit detailed), this counted for only one survey distribution.

Addresses for the hospital where each ICU was located were obtained from national health websites (www.nhs.uk, www.wales.nhs.uk, www.n-i.nhs.uk and www.show.scot.nhs.uk).

7.2.2 Post hospital discharge follow-up and rehabilitation survey

A predominantly closed-question survey, targeted at critical care physiotherapists, was developed evaluating current clinical practice regarding provision of follow-up and available rehabilitation services for survivors of critical illness following hospital discharge, to include detail on content, format, delivery and evaluation of specific rehabilitation programmes, and use of alternative rehabilitation streams where necessary (*Appendix V*).

The survey was divided into three main sections. Initial demographic data were requested regarding the number, level, speciality, and bed-capacity of critical care areas within respondents' organisations. Secondly, detail of availability and physiotherapy involvement in provision of follow-up for post critical illness patients in line with that recommended in NICE CG83 was sought. If follow-up was available, respondents were asked in what format this took, which members of the MDT were involved, and what content was included e.g. exercise capacity recovery, health-related quality of life, psychosocial issues. Specifically, whether follow-up included a functional re-assessment was also asked.

The final section of the survey comprised the largest component. Respondents were requested to indicate whether their institution offered a specific post hospital

discharge rehabilitation programme for survivors of critical illness i.e. separate to generic rehabilitation streams such as supported discharge, intermediate care or similar. If respondents indicated positively, further questions focussed on patient eligibility, structure, format, delivery, content and evaluation of these programmes. Barriers to service provision were sought if none were currently in operation. These were selected from a non-hierarchical list of options that included clinical, pragmatic, managerial and administrative. Respondents were requested to indicate all potential barriers, and then which they considered to be the single, main limiting factor.

Finally in this section of the survey, information was also requested regarding referral of post critical illness patients into alternative rehabilitation streams if no specific services were available e.g. pulmonary rehabilitation, exercise on prescription or similar programmes.

The majority of questions throughout the survey were formatted to allow respondents to select from various tick-box options. These options were not ranked in any order, nor were respondents asked to mark their responses in terms of perceived importance or grading (with the exception of the 'main limiting barrier to rehabilitation' question previously described). Free text space was also available for additional independent detail. At the end of the survey, respondents were asked to provide any other comments regarding any aspect of post critical illness rehabilitation not covered by the survey.

The survey received initial feedback from a clinical academic physiotherapy professor with more than thirty years experience in the field, and piloted using three senior critical care physiotherapists, (ICU clinical experience ranging 7-14years), including one full-time clinician, one clinical academic (50:50 split post), and one full-time academic, all having practiced in critical care within the last 2 years. Constructive critique of the survey design, content, structure, user-acceptability and completion time was requested, following which further refinement of the survey was undertaken.

7.2.3 Participants and survey distribution

In March 2013, the survey and a covering letter of invitation to participate were distributed by post, addressed to the 'Senior Physiotherapist in Critical Care' in the physiotherapy department at each of the identified organisations. Stamped, self-addressed envelopes (SAEs) were provided for return of the questionnaire to the author. Surveys were coded to assist with identification of responses. Throughout the period of survey distribution, a variety of strategies were employed to assist with survey promotion to enhance rates of completion and return. These included use of the interactive physiotherapy respiratory network forum (iCSP, www.iCSP.org.uk), the Association for Chartered Physiotherapists in Respiratory Care (ACPRC) Critical Care sub-group conference and membership email, and circulation of advertisement information via relevant national physiotherapy clinical and research networks (Figure 7-1).

Six weeks following initial survey distribution, a reminder letter was sent to non-responders with a second copy of the survey and further SAEs. A further six weeks later, telephone calls were made to remaining non-responders. Direct contact was attempted with the senior ICU physiotherapist to determine willingness to participate. Respondents were offered the choice of telephone completion of the survey, or electronically via email if details were provided. Respondents were also contacted via email of telephone if there were missing data.

In line with guidance produced by the UK National Research Ethics Service (available at http://www.nres.nhs.uk/) the project was deemed an evaluation of service provision, and therefore ethical approval was not required. Completion and return of the survey was considered indicative of willingness to participate in the survey and implied consent.

7.2.4 Data and statistical analysis

All data was stored in Excel spreadsheets, transcribed from hard copies of returned surveys. Due to the nature of the study and data collected, descriptive statistics were

used to analyse quantitative responses including number, percentage and 95% confidence intervals where appropriate, and additional qualitative review of free-text comments made. A completion response rate of 65% rate was determined *a priori* to provide a representative sample.

7.3 Results

7.3.1 Survey distribution and response

One hundred and eighty-two surveys of the 240 distributed surveys were returned, indicating an overall 75.8% (95%CI 70.4-81.2) response rate. Figure 7-1 summarises the response rate at each stage of survey distribution. Specifically, nearly three-quarters of all surveys distributed to both university teaching (UT) and district general (DG) hospitals were returned (66/85, 75% and 115/155, 74.2% respectively) indicating that the groups of respondents were a representative sample of the original cohort of organisations. One survey was returned blank, with the respondent indicating that they lacked sufficient time for completion of the survey.

7.3.2 Demographics of critical care units in responding organisations

Demographic data from the organisations surveyed are reported in Table 7-1 and Table 7-2. The majority were DG hospitals, with ICUs and HDUs on the whole managing mixed general medical and surgical patient casemixes. A large number of responses reported 'combination' units accepting both Level 3 and Level 2 patients.

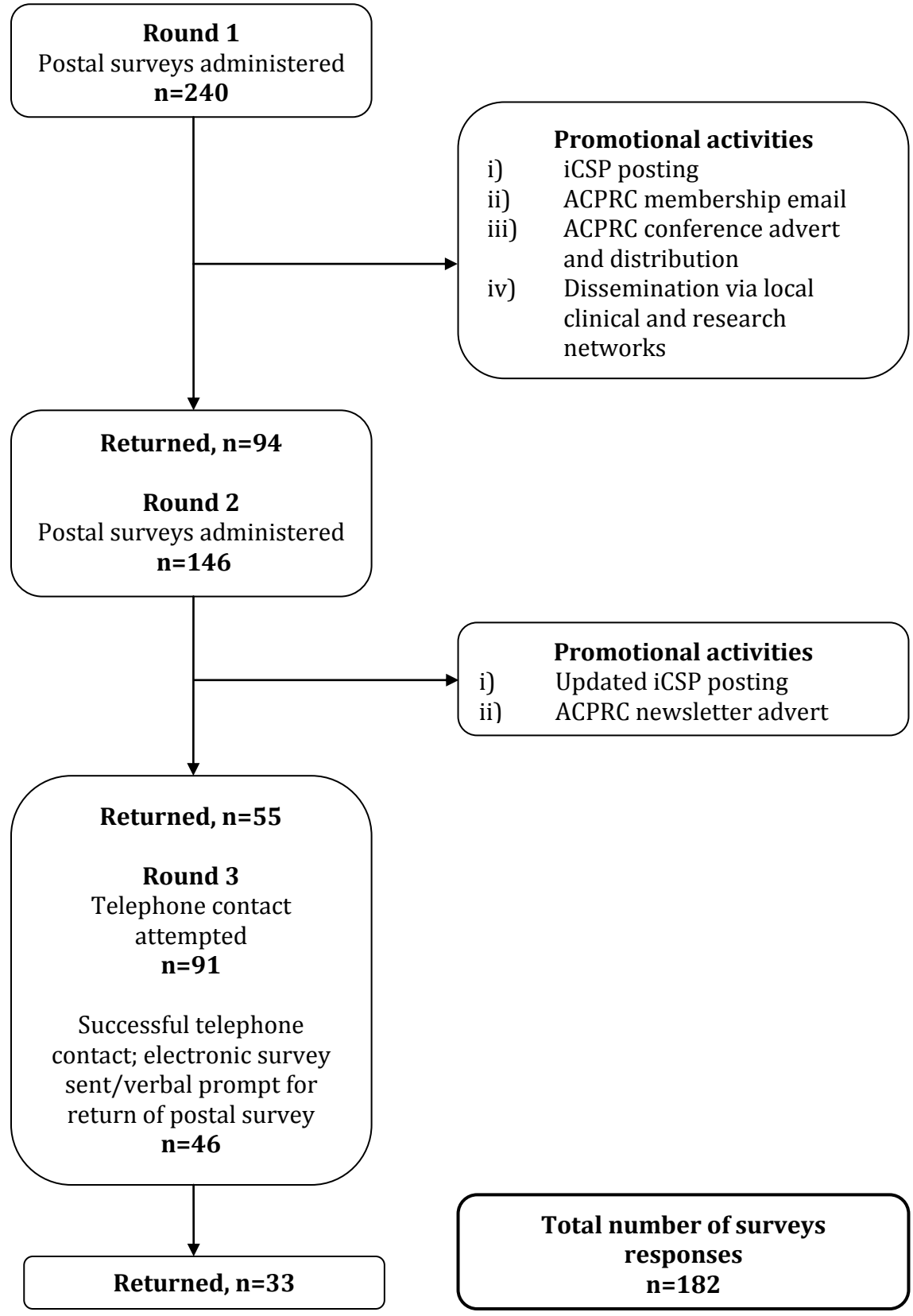


Figure 7-1 Flow-chart of survey distribution stages, response rates and promotional activities

Abbreviations: iCSP = interactive Chartered Society of Physiotherapy. ACPRC = Association of Chartered Physiotherapists in Respiratory Care.

Table 7-1 Classifications of level of care

Level	Classification
0	Patients whose needs can be met through normal ward care in an acute hospital.
1	Patients at risk of their condition deteriorating, or those recently located from higher levels of care, whose needs can be met on an acute ward with additional advice and support from the critical care team.
2	Patients requiring more detailed observation or intervention including support for a single failing organ system or post-operative care and those 'stepping down' from higher levels of care.
3	Patients requiring advanced respiratory support alone or basic respiratory support together with support of at least two organ systems. This level includes all complex patients requiring support for multi-organ failure.

From Comprehensive Critical Care, DH, 2000 [338]

Table 7-2 Demographics of respondent organisations

Characteristic	n (%)
Response rate according to UK country	
England	145 (75.1)
Scotland	20 (87.0)
Wales	12 (80.0)
Northern Ireland	5 (55.6)
Type of hospital	
University teaching	66 (36.5)
District general	115 (63.5)
Total number of Critical Care Units*	
Level 3 (ICU)	112
Level 2 (HDU)	170
Combination Level 3 and 2 units	98
Total number of Critical Care Beds*	
Level 3 (ICU)	1007
Level 2 (HDU)	1090
Combination Level 3 and 2 units	1354
Frequency of reported types of patients admitted to Critical Care Unit*#	
General	230
Surgical	52
Medical	38
Cardiac/Cardiology/Cardiothoracic	35
Neurological	22
Respiratory	17
Trauma	14
Renal	5
Burns	4
Liver	4
ENT	3
Other~	10

n=181 responses (except for response rate according to country, n=192 responses). Critical care units and bed numbers refer to the total number within respondent organisations overall e.g. one organisation may have multiple critical care areas. *n=2 non-responses. #Data presented indicates frequency of reported occurrence of type. Multiple responses could be given. ~Other e.g. haematology, infectious disease, maxillo-facial, vascular.

Abbreviations: ICU = intensive care unit. HDU = high dependency unit. ENT = ear, nose, throat.

7.3.3 Current post hospital discharge rehabilitation research studies

Five respondents reported that available rehabilitation programmes at their organisations occurred as a result of a currently active research study (three studies overall, [190-192]). These responses were considered separately to those from hospitals where services had been 'regularly' implemented, as the aim of the survey was to characterise existing typical clinical practice rather than research activity (Figure 7-2). These five respondents completed the section asking for barriers to offering regular services had the research study not been in implementation at their local site. Further detail regarding the study protocols for these current studies is reported in *Chapter One*.

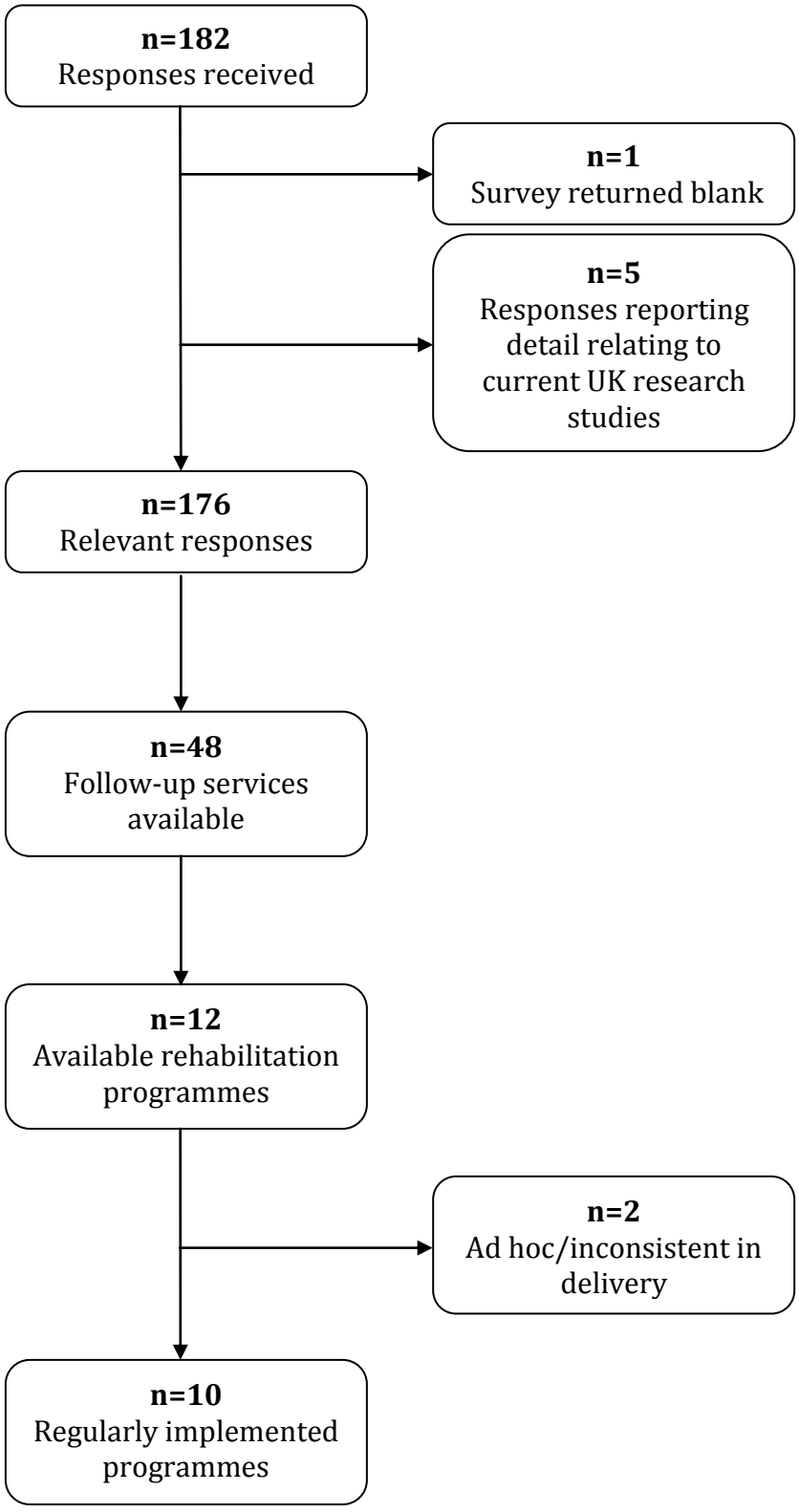


Figure 7-2 Flow-chart outlining available follow-up services and rehabilitation programmes for survivors of critical illness post hospital discharge

7.3.4 Follow-up for survivors of critical illness patients after hospital discharge

Forty-eight organisations (27.3% 95%CI (20.7-33.9)) reported availability of follow-up of post critical illness patients at 2-3months following hospital discharge (Figure 7-1); 66.7% (n=32) of these were from DG hospitals and 33.3% (n=16) from UT hospitals. Forty-five organisations offering follow-up were located in England, two in Scotland, one in Northern Ireland and none in Wales.

7.3.4.1 Format of follow-up

Two respondents did not report details of the format of follow-up. Of the remaining responses (n=46), ICU follow-up clinics were the most frequently reported form of follow-up for post critical illness patients (Table 7-3). 11 respondents reported more than one form of follow-up was available.

Table 7-3 Forms of follow-up reported for survivors of critical illness patients at 2-3months post hospital discharge

Form of follow-up	n (%)
Intensive care unit follow-up clinic	39 (84.8)
Rehabilitation class	10 (21.7)
Other	6 (13.0)
Did not specify	2 (4.3)
Postal survey	1 (2.2)
Telephone call	1 (2.2)
Medical outpatient appointment	0 (0)

n=frequency of reported occurrence out of 46 responses. Multiple forms of follow-up could be indicated.

Other forms of follow-up reported included an informal coffee morning for all ICU survivors (with >7day length of stay) every 3months, a patient support group, rehabilitation delivered as part of physiotherapy outreach, attendance at a local ICU Steps support group, individual physiotherapy referral by lead nurse, and ad hoc appointments with critical care nursing staff. No further detail was given to characterise these services in greater detail.

7.3.4.2 Multidisciplinary team members involved in follow-up

All respondents reporting available follow-up services completed this question (n=48). Forty-three respondents (89.6%) reported that physiotherapists were part of the multidisciplinary team (MDT) involved in follow-up of post critical illness patients. However just under one-third of these (n=13, 30.2%) reported that this was on an ad hoc or referral basis only, at the discretion of other staff involved in the follow-up, and which could be infrequent or occasional. Other MDT members with reported involvement in follow-up are detailed in Table 7-4, albeit in five cases access to critical care doctors, occupational therapists, psychologists or dieticians was also reported to be on a referral basis only. Where critical care nurses were involved in follow-up, this was always on a 'fixed' basis i.e. they were the permanently featured MDT member. Occupational therapists or dieticians were rarely involved in follow-up. The scale of MDT involvement ranged from one member (n=5, 10.4%) to five members (n=1, 2.0%) with three being the most common (n=21, 43.8%). No follow-up service included all listed members of the MDT nor were alternative healthcare professionals mentioned.

Table 7-4 Multidisciplinary teams members involved in post hospital discharge follow-up for survivors of critical illness

Multidisciplinary team member	n (%)
Physiotherapist	43 (89.6)
Critical Care nurse	42 (87.5)
Critical Care doctor	31 (64.6)
Psychologist	10 (20.8)
Dietician	2 (4.2)
Occupational therapist	2 (4.2)

n=frequency of reported occurrence out of 48 responses. Multiple team members could be listed

7.3.4.3 Content of follow-up services

One response was blank for whether follow-up services included a functional reassessment based on previous assessment conducted at the time of hospital discharge. Of the remaining 47 responses, 20 (42.6%) reported that a functional re-assessment was performed, and 27 (57.4%) that it was not. Table 7-5 presents other

aspects included in follow-up services, with health-related quality of life (83.3%) and psychological status (81.3%) being the most frequently reported items. Exercise capacity and nursing-related issues were included in approximately half of cases.

Nine responses included other comments such as that follow-up adopted a "...discussion of the common side-effects of critical illness e.g. reduced functional capacity, joint pain, anxiety, nightmares and hallucinations" and "...formal physio follow-up from appropriate services e.g. musculoskeletal" as deemed necessary. Other topics listed as being discussed at follow-up included sleep, mood, carer concerns, goals for work, tracheostomy site/wound management.

Table 7-5 Content of post hospital discharge follow-up for survivors of critical illness

Content of follow-up	n (%)
HRQL	40 (83.3)
Psychological status	39 (81.3)
Medical status	34 (70.8)
Nursing-related issues	29 (60.4)
Exercise capacity	28 (58.3)
Diet/nutrition	24 (50.0)
Other	9 (18.8)

n=frequency of reported occurrence out of 48 responses. Multiple content could be listed.

Abbreviations: HRQL = health-related quality of life

One response reported that follow-up was "...guided by recommendations by iCAN-UK. Our assessments are problem-based". Another indicated that content was modelled on educational session typically included in pulmonary rehabilitation classes, and a further that follow-up content was "...patient-dependent". One response highlighted that whilst all the aforementioned topics were discussed in follow-up, outcome measures were not used to formally assess these parameters. Furthermore one response described follow-up as "...more of a general chat regarding coping at home and reaching goals".

7.3.5 Rehabilitation programmes for survivors of critical illness post hospital discharge

7.3.5.1 Availability, leadership, and enrolment

Twelve organisations reported a rehabilitation programme available following hospital discharge for post critical illness patients (6.8% 95%CI (3.1-10.5)) (Figure 7-2). Two reported that their programme was available on an ad hoc or inconsistent basis – these are reported separately. Of the remaining ten programmes implemented on a regular basis, all were based at organisations in England. All had also reported offering a follow-up service, with eight of these in the form of an ICU follow-up clinic. Four organisations offering regular rehabilitation programmes were UT hospitals, and 6 were DG hospitals.

Physiotherapists led all of these available rehabilitation programmes. In the majority of cases (n=9) this was a senior ICU physiotherapist (median (IQR) Agenda for Change banding 7 (6-7), median (IQR) duration ICU experience 7.0 (4.0-13.0)years), albeit full details of grade and experience were not provided by all respondents. A rehabilitation physiotherapist led one rehabilitation programme. One programme reported additional involvement of an occupational therapist and fitness instructor, three others included a critical care nurse. No other multidisciplinary team members were reported as being involved in any of the rehabilitation programmes.

There were limited data provided regarding detail of enrolment of patients into rehabilitation programmes (Table 7-6). Both the category of eligibility criterion and specific detail of the assessment measure were requested from a pre-defined list e.g. duration of mechanical ventilation (category) and >48hours (assessment measure), and free text was also provided for independent detail. No detail of eligibility criteria was reported for one rehabilitation programme.

Table 7-6 Detail of enrolment criteria into post hospital discharge rehabilitation programmes

Eligibility criteria	n (%)	Detail of assessment measure
Duration MV	7 (70.0)	>5 days; >4 days; >3 days; 48hours
ICU LOS	3 (30.0)	>5 days; >4 days
Hospital LOS	2 (20.0)	"lengthened"
PF: ICU discharge	2 (20.0)	"reduced from pre-admission"
Muscle strength: ICU discharge	2 (20.0)	No detail provided
Exercise capacity: ICU discharge	2 (20.0)	No detail provided
HRQL: ICU discharge	0	-
PF: hospital discharge	4 (40.0)	No detail provided
Muscle strength: hospital discharge	3 (30.0)	No detail provided
Exercise capacity: hospital discharge	3 (30.0)	No detail provided
HRQL: hospital discharge	1 (10.0)	No detail provided
All patients eligible	1 (10.0)	"any ITU stay"
Other	2 (20.0)	"those with profound weakness or functional limitation regardless of LOS"; "screen for low or high risk throughout ICU/hospital stay. If high risk, exercise plan, goals and rehab class if suitable. All plus 2 day ICU are automatically sent SF8 and depending on score, either 1:1 or group follow-up"

n=10 responses. Multiple criteria could be reported per response.

Abbreviations: ICU/ITU = intensive care/therapy unit. MV = mechanical ventilation. HRQL = health-related quality of life. LOS = length of stay. PF = physical function. SF8 = Short Form-8 (a health-related quality of life survey).

7.3.5.2 Format of delivery

Nine rehabilitation programmes were hospital-based and one was home-based. Patients exercised under supervision in four programmes, and with a combination of supervised and independent exercise in the remaining six. Only one programme used an accompanying rehabilitation manual, however, three others reported providing printed, individualised home exercises for patients. Detail of any accompanying rehabilitation manual or alternative material was not reported for one programme.

All programmes were stand-alone rehabilitation programmes designed for post critical illness patients, and not combined with existing disease-specific services such as pulmonary or cardiac rehabilitation. Four commenced immediately following

hospital discharge, 1 within one week of discharge, three within two weeks, and one each within one month and at 2-3months respectively following hospital discharge. In addition it was reported that for two programmes, rehabilitation could commence whilst patients were still on the wards, and five reported that the exact starting point following hospital discharge depended on patient fitness and readiness. Only one (8.3%) rehabilitation programme reported a waiting list of two weeks.

7.3.5.3 Structure

The number of sessions included in rehabilitation programmes varied greatly, ranging from 6 to 12 excluding additional assessment sessions. Three programmes had the capacity and/or flexibility to allow patients to continue until certain goals had been achieved or further time was required to achieve an individual's target physical functional level. Number of sessions was not reported for two programmes.

Typically sessions ran weekly (7 programmes) or twice-weekly (3 programmes); no other frequency of sessions was reported, and all programmes included sessions of 60mins duration. Eight programmes were 'rolling' in operation programmes, meaning patients could start and finish the programme at any point in time, and one was stand-alone, such that cohorts of post critical illness patients all started and completed programmes simultaneously. This detail was not reported for one programme.

Reported group size and staff:patient ratio across rehabilitation programmes was also highly variable. One programme incorporated a 1:1 staff:patient structure, whilst another adopted a flexible approach that depended on the complexity of the patient and individual rehabilitation needs. Across the remaining programmes group sizes ranged from 5 up to 14, with approximately one qualified staff member for every 3 patients. Most programmes adopted patient-specific exercise plans (n=7) whilst three reported that patients exercised in a pre-determined circuit.

7.3.5.4 Content

All rehabilitation programmes included an exercise component, involving a combination of cardiovascular, strength, balance and functional activity. Table 7-7 provides further details of frequency of inclusion of specific types of these exercises. Nine programmes utilised at least two different forms of exercise prescription during the programme. Clinician judgement was the most commonly utilised form in seven programmes, followed by results of walking tests (n=6) and physical function assessment (n=5). Physiological parameters such as target perceived rate of exertion and heart rate, and results of balance assessment were used relatively infrequently (n=2, n=2, n=1 programmes respectively). No programme incorporated use of the repetition maximum principle to prescribe exercise.

Table 7-7 Detail of exercises included in post hospital discharge rehabilitation programmes

Category of exercise	Specific exercise	n (%)
Cardiovascular	Static bike	10 (100.0)
	Step-ups	9 (90.0)
	Treadmill	7 (70.0)
	Cross-trainer	2 (20.0)
Strength	Lower limb	10 (100.0)
	Upper limb	10 (100.0)
	Theraband/resistance	9 (90.0)
	Free weights	7 (70.0)
Balance	Dynamic	9 (90.0)
	Static	5 (50.0)
Functional	Sit-to-stand	8 (80.0)
	Walking	6 (60.0)
	Timed Up And Go	2 (20.0)

n=frequency of reported occurrence out of 10 responses. Multiple exercises could be listed/response.

Similarly, all programmes included at least two forms of patient monitoring during exercise sessions, based on a range of physiological and clinical factors. Seven programmes reported use of target rates of perceived exertion, 4 used oxygen saturation levels, and 3 monitored heart rate. Contrastingly, patient-related

parameters were also adopted - 8 programmes monitored exercise based on verbal patient feedback, 6 based on clinician judgement of the patient, and 2 based on visual analogue scales. Four programmes reported incorporating reassessment of baseline measures as a form of monitoring.

Less than half of programmes included an education component (n=4). A range of topics were covered including exercise, stress management/relaxation, nutrition, return to work, energy conservation, medications, recovery following critical illness, smoking cessation, managing breathlessness and breathing control, delivered predominantly by physiotherapists but with additional input from occupational therapist and nursing colleagues.

7.3.5.5 Evaluation

Table 7-8 reports the category and detail of outcome measures used to evaluate rehabilitation programmes. Exercise capacity and health-related quality of life outcome measures were the most commonly utilised.

Table 7-8 Outcome measures used to evaluate post hospital discharge rehabilitation programmes

Outcome measure	n (%)	Detail of outcome measure
HRQL	10 (100.0)	SF-36, HADS, EQ5D, FIM, SF-8
Exercise capacity	9 (90.0)	6MWT; ISWT
Other	3 (30.0)	Achievement of patient-specific goals; BMI; Impacts of Events Score
Functional	2 (20.0)	TUAG; patient-specific goals
Strength	1 (10.0)	2 minute step-ups
Mental/cognitive	0	-

n=frequency of reported occurrence out of 10 responses. Multiple outcome measures could be reported/response.

Abbreviations: HRQL = health-related quality of life. 6MWT = Six Minute Walk Test. ISWT = Incremental Shuttle Walk Test. SF-36 = Short Form 36 v2. HADS = Hospital Anxiety and Depression Scale. EQ5D = EuroQol 5 Dimensions. FIM = Functional Independence Measure. SF-8 = Short Form 8. TUAG = Timed Up And Go. BMI = body mass index.

7.3.5.6 Barriers to offering post hospital discharge rehabilitation programmes

Respondents were requested to report barriers to delivery of post hospital discharge rehabilitation programmes in their organisations as part of routine clinical practice for post critical illness patients from a non-hierarchical list that included clinical, pragmatic and managerial and administrative options. From those selected, respondents were also asked to confirm the main reason. Out of a potential 171 responses from organisations (i.e. excluding one blank response and the ten regularly implemented rehabilitation programmes in operation), there were seven non-responses to both parts of this question, and a further 8 non-responses to specifying the main barrier. Table 7-9 reports frequency of reported barriers to post hospital discharge rehabilitation programme service provision. Ninety-one percent (n=149) of respondents reported lack of funding as one barrier to offering post hospital discharge rehabilitation programmes, and three-quarters reported lack of staff numbers. A minority of respondents reported that a lack of evidence was a barrier to implementing a post hospital discharge rehabilitation programme. 'Time constraints' was the single other barrier listed. Ten respondents reported only one barrier, 33 reported two reasons, and 120 reported multiple (>2) barriers.

Table 7-9 Barriers reported to offering post hospital discharge rehabilitation programmes

Barrier	n (%)
Lack of funding	149 (90.9)
Lack of sufficient staff	128 (78.0)
Resources prioritised to other patient groups/clinical areas	71 (43.3)
Not considered required service at managerial level	66 (40.2)
Lack of available space	50 (30.5)
Insufficient patient numbers to justify	35 (21.3)
Extra-contractual (out-of-area) patient caseload	15 (9.1)
Lack of trained staff	13 (7.9)
No evidence	4 (2.4)
Not sure what to include in a programme	2 (1.2)
Other	1 (0.6)

n=frequency of reported occurrence out of 164 responses. Multiple barriers could be listed.

Lack of funding was also reported as the main barrier to service provision (n=99, 63.5%), and this far exceeded any other barrier (Table 7-10). 'Not required at managerial level', 'Lack of sufficient staff' and 'Insufficient patient numbers' were the other main barriers most frequently reported.

Table 7-10 Main barriers reported to offering post hospital discharge rehabilitation programmes

Main barrier	n (%)
Lack of funding	99 (63.5)
Not considered required service at managerial level	22 (14.1)
Lack of sufficient staff	17 (10.9)
Insufficient patient numbers to justify	11 (7.1)
Resources prioritised to other patient groups/clinical areas	4 (2.7)
Lack of available space	2 (1.3)
Other (time constraints)	1 (0.6)
Not sure what to include in a programme	0 (0.0)
Lack of trained staff	0 (0.0)
Extra-contractual (out-of-area) patient caseload	0 (0.0)
No evidence	0 (0.0)

n=frequency of reported occurrence out of 156 responses.

A number of free-text comments were made in relation to this question, and further elucidate the themes of funding restriction, resource allocation/availability (including staffing) and strategic management priorities and policy as key limiting factors in implementing post hospital discharge rehabilitation programmes (Note: words in italics added by the author for full interpretation):

> "...we at times struggle to fight for staff for in pt rehab (*in-patient rehabilitation*) let alone fight for a budget for op (*out-patient*) care
>
> "...we run a voluntary f-u (*follow-up*) clinic but have had to withdraw the rehab (*rehabilitation*) and psych (*psychology*) elements due to no (sic) support from therapy managers
>
> "...despite extensive work the business case was declined
>
> "...a rehab (*rehabilitation*) programme was run for 12m using charitable funds money. Ongoing funding was not secured as it was not deemed a Trust priority

"...historically no service available, no need established by current ICU services

"...and not considered required at managerial level; Some years ago charitable funding was available to open follow-up clinic to include rehab (*rehabilitation)* service but Trust board refused the 2 year funding as they could not commit to continuing to fund the service once the charitable monies expired. So the reason we didn't introduce the service at that time was a mix of funding and managerial issues. Currently I would think staffing would be another issue.

"...previously ran post ICU rehab (*rehabilitation*) class but had to stop because reduced staffing (prioritising in-pt) and difficult to get numbers (no transport provided)

"...The main barriers to this aspect are time constraints, lack of staff and funding alongside limited knowledge of potential co-morbidities following ICU stay. Critical Care follow up clinics do not take place in an adequate time frame in this trust and as such many people do not attend, therefore we are missing potential problems. Additionally the clinic is not an MDT run clinic, limiting clinical identification of potential problems.

"...absence of vertical integration of health and social care

"...not so much not considered as required - sure the team believe it's required just not enough resources

"6.5WTE PT (*6.5 whole-time equivalent physiotherapists*) in team covering 7 different ward specialities, 3x critical care areas, resp o/p (*respiratory out-patients*), resp pts (*respiratory patients*) in A&E/admissions

Other comments described the interaction between acute and primary care services, which in some cases offer a route for ongoing rehabilitation input, and clinical and logistical factors for consideration in determining need for specific critical care services:

"...inpt (in-patient) and outpt (out-patient) services are provided by two separate organisations, therefore although the inpt (*in-patient*) team would like to provide a service the community team will not lend support

"...pt (*patient*) needs met by other community services available

"...not sure if we would have individual class therefore combined with PR (*pulmonary rehabilitation*); we would like to set one-up

"...numbers are very small and tends to be post-op (*post-operative*); back to baseline 5/7 (*at five days*). not seen need to provide service separate to our IRS (*in-patient rehabilitation or integrated respiratory service*)
"...We have a follow up clinic run by our CCORT (*critical care outreach team*), but no physical rehab (*rehabilitation*) post D/C (*discharge*) home (unless needing regular community physio (*physiotherapy*) input)

"...very structured in hospital critical care rehab (*rehabilitation*) service to maximise pt (*patient*) status at hospital d/c (*discharge*), has significantly reduced LOS (*length of stay*), readmissions to critical care, QOL (*quality of life*) scores and ongoing co-morbidity/health problems. Insufficient numbers for group rehab (*rehabilitation*) specific to CCD (*critical care disease*) post d/c (*discharge*)

"...patients who need long-term rehab (*rehabilitation*) are followed up by community staff

"...we use PR (*pulmonary rehabilitation*) programme for many post ITU patients

"...cardiac patients go to CR (*cardiac rehabilitation*)

7.3.5.7 Utilisation of alternative rehabilitation streams

The majority of respondents (98/171, 57.3%) reported that in the absence of a specific post hospital discharge rehabilitation programme for survivors of critical illness at their organisation, these patients were referred into alternative rehabilitation streams, including pulmonary and cardiac rehabilitation (albeit solely for those patients with cardiac diagnoses), and various community-based services (Table 7-11). Seventy-two respondents (42.1%) reported this approach was not employed, and there was one non-response.

Table 7-11 Alternative rehabilitation streams used for post critical illness patients following hospital discharge

Rehabilitation stream	n (%)
Pulmonary rehabilitation	62 (63.3)
Other -	59 (60.2)
Community therapy	*41 (69.52)*
Community Hospital	*13 (22.0)*
Intermediate Care Teams	*12 (20.3)*
Patient-guided	*7 (11.9)*
Domiciliary rehabilitation	*6 (10.2)*
Outpatients	*6 (10.2)*
Exercise on prescription	42 (42.9)
Cardiac rehabilitation	38 (38.8)
Community gym session	21 (21.4)

n=frequency of reported occurrence out of 98 responses. Multiple options could be listed. Note there may be some overlap between various other community services depending on local terminology.

7.3.5.8 Non-regular rehabilitation programmes

One of the non-regular programmes was described as "...ad hoc gym sessions run by the ITU (intensive therapy unit) physios..." – no further detail was reported on this. The second programme was reported as being run by an ICU physiotherapist, AfC Band 7 with 13 years ICU experience. Enrolment criteria included physical function, muscle strength and exercise capacity measured at both ICU and hospital discharge although no specific detail of assessments measures was reported to characterise these criteria further. This programme was offered as either home, or hospital or community based, "...depending on requirements – ICU staff may supervise/direct other PT (physiotherapy) staff...".

Patients exercised under supervision and independently, and their programmes were accompanied by handouts of their individual exercises. This was a stand-alone programme that commenced immediately following hospital discharge, as soon as feasible for patients, and reported no waiting list. Sessions of 40minutes duration could be weekly or twice-weekly, and the overall programme duration lasted "...as required to reach (*the patient's*) desired functional/physical level...". Exercises included cardiovascular, upper and lower limb strengthening, balance and functional

activities. Exercise prescription was based on the results of walking tests, physical function and balance assessments, and clinician judgement. Progression and monitoring of exercise incorporated the Borg score (for perceived exertion), patient verbal feedback and clinician observation/judgement. There was no education component to this programme.

Programme evaluation included strength-based outcome measures (Oxford grading scale), exercise capacity (Incremental Shuttle Walk Test), and functional performance (Timed Up And Go test). The respondent for this non-regular rehabilitation programme concluded by giving the following comments:

> "...we've always provided physical/functional rehab (*rehabilitation*) to our critical care patients post discharge but numbers are relatively low so provide individual programme based upon clinical need as and when required. ICU physio usually required to delegate rehab delivery to TI (physio support worker) or local physio staff but oversee programme and progression. If appropriate patients may also be slotted into next available pulmonary rehab programme, but prefer to provide individual gym based exercise programme if no preceding lung condition.

Both respondents for the organisations running non-regular rehabilitation programmes completed the question asking for information on barriers to offering a regularly implemented rehabilitation programme.

7.4 Discussion

These data from the first comprehensive UK survey highlight the limited implementation of NICE CG83 and the poor delivery across the UK of post hospital rehabilitation services for survivors of critical illness. Indeed, of one hundred and eight-two surveys returned, less than one-third of all organisations provided any form of follow-up for these patients. Of major clinical concern is that only 5% of respondents reported provision of a regular rehabilitation programme, a major focus of NICE CG83. Lack of funding was the most frequently reported and main barrier to service availability. Furthermore lack of managerial support for this type of service and prioritisation of resource allocation to other clinical areas were reported as barriers by over 40% of respondents. Whilst survey data can have a number of potential limitations, in particular bias introduced through non-response, the current

study benefited from a high response rate achieved through utilisation of a variety of promotional activities and diligent follow-up to enhance completion and return. These data indicate that inadequate clinical infrastructure exists for hospitals and community teams to successfully adhere to NICE CG83. The limited impact of NICE guidance on clinical practice is not unique to critical care rehabilitation and is, rather disappointingly, a theme observed in other healthcare areas that have been subject to the development of national guidance.

7.4.1 Clinical interpretation

7.4.1.1 Implementation of NICE CG83 across the UK

Data from this survey indicate a lack of implementation of NICE CG83 guidelines with a limited number of follow-up services available post hospital discharge, and even fewer rehabilitation programmes. This could have reflected poor motivation on the part of clinicians to actively engage in the delivery of the recommendations. However, the key barriers to service delivery were reported as lack of funding, limited resources and infrastructure with reduce priority at managerial level. In the current climate of the National Health Service (NHS), such obstacles to the application of NICE CG83 are at either a clinical commissioning or clinical operational level, or both, rather than at the level of the clinicians. This theme is echoed in the content of free-text comments by respondents that highlighted frustrations and disappointment at the difficulty in securing support for such services. Interestingly, the paucity of data to support the effectiveness of post ICU rehabilitation was not perceived as a barrier by the vast majority of clinicians (only 4% reported this as a potential barrier), and highlights the complexities in the management and clinical delivery of a critical care rehabilitation service. A conflict between clinicians, managers and commissioners has developed as the lack of high level clinical evidence supporting NICE CG83 provides a major challenge to the funding of a critical care survivor rehabilitation service by both managers and commissioners. At present the evidence base for post hospital discharge rehabilitation interventions is slowly developing, as described in detail in *Chapter 1*.

7.4.1.2 Alternatives to specific post hospital discharge rehabilitation programmes for survivors of critical illness

Rehabilitation for survivors of critical illness represents a challenge for researchers, designing and evaluating complex interventions in a complex patient group [339]. Further translational studies and clinical trials are required to develop the evidence-base. Until such data are available, the unmet clinical need will remain evident and unaddressed in this patient population. Referral of patients into established rehabilitation programmes, such as cardiac and pulmonary rehabilitation, offers one potential resolution with over 50% of respondents reporting the use of alternative rehabilitation programmes for critical care survivors. This may further be influenced by the designated speciality of the ward destination of patients following ICU discharge. Indeed, the most recent guidelines for pulmonary rehabilitation advocate an individualised approach to patient management [287], and these interventions could easily be adapted for patient recovering from critical illness, albeit that additional referrals may place an increased burden on such services. Furthermore, whilst valuable resources, these programmes are disease-specific and may not fully address the range of impairments demonstrated by survivors of critical illness as part of the 'post intensive care syndrome' [125].

7.4.1.3 Clinical usefulness of post ICU clinics

The vast majority of follow-up services (84.8%) in the current survey were conducted in the form of an ICU follow-up clinic. These were first profiled in the late 1990s and early 200s following updating of the NHS Agenda for critical care [329, 338, 340], and have been reported by patients to represent a valuable contribution to their physical, emotional and psychological recovery providing them with a source of information and support to understand their ICU experience [341]. However previous survey data have indicated poor implementation of these early recommendations with a low prevalence of available follow-up clinics [329], and trials data have failed to demonstrate clinical effectiveness or cost benefit [184].

With reference to NICE CG83, the management of ICU patients beyond ICU discharge requires closer attention. An alternative strategy for the conduct and purpose of post ICU clinics would be to robustly monitor over time the trajectory of recovery of ICU survivors with onward referral into specific speciality care where identified as required. This would require a coordinated multidisciplinary team approach, lacking in the services reported in the current study. Wide variability in responses regarding post hospital discharge rehabilitation programmes for ICU survivors severely limits any consensus on the optimum approach for these services. The marked heterogeneity of the patient population makes it increasingly likely that a bespoke, individualised approach, akin to personalised medicine, may be more appropriate.

7.4.1.4 Barriers to implementation of clinical guidelines

Implementation of and adherence to clinical guidelines can be inconsistent [342-345]. In a systematic review examining this, Cabana *et al* [346] identified a framework of seven factors influencing successful uptake of guidelines – lack of awareness, lack of familiarity, lack of agreement, lack of self-efficacy, lack of outcome expectancy, inertia of previous practice and external barriers. These are similar to the model outlined by the Scottish Intercollegiate Guidelines Network (SIGN) who defined internal barriers to the guideline itself (which can be addressed by development in accordance with a robust methodology) and external barriers relating to the clinical environment and specific local circumstances [269].

Lack of awareness and familiarity were assumed not to be major limiting factors. Whilst the current study did not specifically ask regarding this, NICE CG83 has been in circulation since 2009 and much work in the field of early mobilisation and rehabilitation practice for ICU survivors has appeared in the literature in the intervening time [141, 142, 146, 163, 172, 176, 177, 180]. Furthermore, 83% of lead ICU physiotherapists were reported as aware of the guideline in a previous survey [200] and the researcher (BC) has empirically observed significant discussion around the guidelines and sharing of ICU rehabilitation practices on the UK professional physiotherapy online forum (www.i-csp.org.uk).

In addition, whilst also not specifically surveyed, there were no responses indicating lack of agreement from clinicians with NICE CG83. Only 2 respondents reported uncertainty as to what to include in a programme was a barrier (self-efficacy). Whilst qualitative comment provided by respondents was not analysed formally there was no indication of a theme suggesting clinicians did not perceive that rehabilitation would be of benefit (lack of outcome expectancy), albeit a minority of respondents reported that lack of evidence was a barrier. This suggests that for these respondents in particular it was important to have robust grounds to support offering services, and proof of effect was required prior to local implementation.

Inertia of previous practice reflects a lack of motivation or inability to overcome previous practice. That a large proportion of those clinicians unable to offer specific rehabilitation service for post ICU patients, instead utilised alternative forms of rehabilitation suggests this was not evident in the current study, and that there was a willingness to consider other options to address the issue of availability of rehabilitation services. By far the greatest challenge to implementation of NICE CG83 were external factors, which can broadly be categorised further into guideline-related, patient-related and environmental-related [346] and may encompass challenges associated with infrastructure, organisation, resources and local attitudes and practice [269].

The relatively broad nature of the guideline, encompassing three distinct stages of the patient pathway and the transition between each, and lack of specific detail challenge its translation into clinical practice. Given the current economic climate within the NHS it is increasingly difficult to secure funding to develop and establish services without existing evidence and where the remit is broad and relatively undefined. Lack of prioritisation from senior management was also influential, with resources directed to other clinical services. There have been no data published examining the patient perception of the importance of NICE CG83, or indeed awareness of the guideline at all. However at an organisational level, patient-related barriers were reported in the current study including demand for services, tertiary referral status and geographic residency. In the future a 'joined-up' network of services across regional areas could facilitate the transition of patients between teams and

organisations to ensure a seamless pathway of care, and a more co-ordinated system of working between ICU and rehabilitation clinicians, facilitated by offering patients a more individualised approach to their rehabilitation requirements. Examining the rehabilitation infrastructure in existence in other disease pathologies such as stroke (which also has guidelines to direct practice) may also provide a useful template for addressing some of the factors currently challenging NICE CG83 implementation [347].

This is the first survey to investigate reasons behind failure to implement such a national guideline and the current data offer significant insight into the requirements necessary for successful clinical application of recommendations designed to enhance patient care. Essentially limited guideline detail, staff infrastructure, organisation and resources were the main restrictions to implementation [346]. Whilst the goals of NICE CG83 were important and raised the profile of this area of clinical practice the influence will be short-lived without further investment in support systems at operational and staffing level. Disappointingly, this scenario appears to be mirrored in other common clinical conditions. Although evidence supports the use of early pulmonary rehabilitation (PR) following acute exacerbation of chronic obstructive pulmonary disease (AECOPD) to enhance exercise capacity, health status and reduce hospital readmissions [187, 188, 287, 348], recent data suggest that only one-third of eligible patients are referred to early PR programmes and less than 10% of all hospital discharges for AECOPD complete early post-hospitalisation PR [327]. This implementation failure is also observed following NICE guidance on the management of obstructive sleep apnoea [349] with a recent national mapping exercise highlighting a significant mismatch between predictive healthcare requirements, based on prevalence of known associated risk factors, and delivery of related services [328]. Furthermore, the 2012 NHS Atlas of Variation in Healthcare for People with Diabetes [326] revealed substantial numbers of patients were not in receipt of the basic clinical standards of care. The barriers to the implementation of these guidelines are specific to each clinical area, but those generic ones such as lack of adequate funding and resources need to be considered carefully. However, it must be highlighted that robust clinical trial and other data are required to support a guideline

if it is to be commissioned within the NHS and delivering a guideline prematurely will lead to implementation failure, despite major enthusiasm by clinicians.

7.4.2 Comparison with previous studies

There is little published data available regarding availability of follow-up services for survivors of critical illness. Two previous surveys have reported a low incidence of ICU follow-up post hospital discharge; the National Outreach Survey estimated 41 ICUs (12%) provided outpatient services (cited by [329]), a figure that was subsequently reported as being somewhat greater in a 2006 survey by Griffiths *et al* [329] at 30% (80 ICUs). The current study found that 48 (27.3%) organisations reported an available follow-up service. Whilst it is possible that an actual decline in services may have occurred in the intervening years, especially in view of published data challenging the effectiveness of follow-up clinics in improving health-related quality of life in ICU survivors and cost-effectiveness [184], it is also not possible to ensure that all datasets surveyed the exact same populations in order to make firm comparison. Data regarding ICUs originated from the central database available at the time of surveying but this may provide a source of variability particularly if not kept up-to-date accurately. Furthermore the current study directed surveys to physiotherapy clinicians, whereas previously medical and nursing staff were identified as recipients. If physiotherapists were not directly involved in follow-up, then this service may not have been reported thus influencing results.

In keeping with the NHS climate at the time of surveying, Griffiths *et al* [329] assumed clinics to be the only route for follow-up, and certainly this format was the most prevalent reported in the current survey. However in more recent times additional options have become available including rehabilitation classes, postal survey, telephone call and informal support groups. Additionally the current survey asked about multiprofessional involvement, in contrast to the sole involvement of only medical or nursing staff in the past. Both surveys reported that lack of funding was the major barrier limiting service availability.

Two previous surveys have reported adherence to NICE CG83 albeit limited in content and geographical distribution. Appleton and colleagues [200] conducted a survey solely in Scotland and directed towards both medical and physiotherapy staff. These authors attempted to encompass the entirety of the guidelines with content including rehabilitation practice in ICU, on the ward and post hospital discharge. As a result the latter stage is significantly brief and data not comparable to the current study, which focussed specifically on post hospital discharge in greater detail. Perhaps whilst more time-consuming to complete this provides greater characterisation of services available at this stage of patient recovery. Notably in the former survey, physiotherapy staff were targeted to respond to questions on providing follow-up at 2-3months and use of outcome measures to assess physical dimensions of rehabilitation following hospital discharge [200], mirroring the target respondents in the current survey. A recent survey by Berry et al [201] aimed to examine all recommendations within NICE CG83 but distribution excluded key regions, and further missing data limited data analysis and findings. Nonetheless at the post hospital stage of recovery, adherence to NICE CG83 was found to be severely lacking.

The current survey response rate of 76% is at the higher end of the range reported by all these surveys, and greater than a large number (22-86.5%). The current study adopted a similar protocol with regard survey design and target population to the majority of these surveys i.e. a postal survey distributed to senior physiotherapy clinicians, which appears to anecdotally be considered the most effective strategy for such surveys according to this literature pool. However further comparison of results is limited by the differing purpose and content of these surveys relating to various aspects of ICU patient management across the recovery pathway.

7.4.3 Critique of the method

7.4.3.1 Designing the optimum survey process

A postal survey was the format of choice for the current study due to the large sample size of the target population (n=240) and its geographical distribution [350]. Postal surveys are cost-effective and can be simpler and quicker to distribute than

alternative forms such as telephone interviews [351-353]. Furthermore they have been shown to result in greater response rates compared to telephone interviews [352], and email format albeit with a longer time to response [354]. In addition postal surveys offer all recipients the opportunity to respond, whereas email or internet formats exclude those without adequate computer and internet access. However an email or internet-based platform would have been restricted in the current study due to lack of available electronic contact details for named critical care physiotherapy clinicians, and where postal distribution offered a more standardised approach for monitoring and identifying respondents. Return of a completed survey was taken to represent consent to participate in the study, and those not wishing to participate simply failed to return the survey, similar in principle to an 'Active Decline' approach which has been shown to be associated with higher response rates, improved time-efficiency and cost-effectiveness [353].

Survey formatting is an important consideration in design – questions should be easy to read in a clear font and layout, be numbered, organised, structured, unambiguous, and specific; responses should clearly relate to the question but can be either open-ended inviting free text, or closed, with fixed choices (in the current survey, in the form multiple tick-box options) [355-357]. In addition factors such as printing single- or double-sided can influence appearance to the reader and therefore response likelihood [351], although practical and financial resources may determine the extent to which researchers can focus on these aspects. The current survey adopted a number of these factors, and furthermore included a credible, personalised cover letter that outlined the purpose and aims of the survey [355-357]. Furthermore the current survey also underwent a review process with three senior physiotherapy clinicians and clinical-academics for critique on questionnaire structure, clarity, layout and ease and timing of completion. Based on this feedback, further refinement was made to the survey prior to wider distribution. Whilst it could be argued that a larger pilot sample could have been helpful at this stage, it was considered this may place a greater burden on those respondents who may be required to repeat completion during the main round, especially if significant changes had been made.

Stamped addressed envelopes were included with all mailed surveys, a highly recommended strategy for facilitating response [350, 355, 356]. Following round three of postal distribution, non-responders were contacted via telephone and requests made for either completion via telephone or email (if details were provided). Contacting non-responders in this way was more feasible at this stage due to smaller numbers, as the relative expense and time required for this process would have been prohibitive during earlier rounds of distribution. However only 50% of non-responders were contactable which demonstrates a limitation with the telephone approach. Hocking *et al* [352] found similar difficulties with achieving successful telephone contact to senior clinicians, with calls restricted by fielding from secretarial staff, and challenges locating the correct clinician when individual names were unknown. Nonetheless this process still resulted in a conversion rate of 36% of non-respondents in the current study.

The ICUs identified for inclusion in the current survey originated from two national databases, ICNARC and SICSAG, in order to provide a comprehensive target population. Specialist-only and private ICUs were excluded as it was considered that patient cohorts at these ICUs may have pathology-specific rehabilitation requirements and existing pathways in place, be extra-contractual (including overseas) and be influenced by different funding and resource streams due to their status. It was anticipated that the population identified through this process would be representative of general ICUs across the country; whilst it is possible that some ICUs may not be registered on these databases, this was considered unlikely. However information regarding rehabilitation services at excluded organisations may add value in a future survey to provide a more thorough reflection of rehabilitation service provision.

As mentioned above, there is currently no central registry of respiratory critical care physiotherapists working in the UK that would include contact details, grade and experience. Hence it was not possible to direct the current survey to any named individual at each organisation, instead a generic title of 'Senior Physiotherapist for Critical Care' was used and the survey directed to the physiotherapy department at each organisation. It was thought that senior, experienced clinicians would be able to

comment not only on the availability and detail of any services, but also on potential barriers preventing service availability. However it is acknowledged that the survey may have been completed by more junior staff depending on local staffing arrangements, perceived importance and the time constraints of senior clinicians.

The current study was physiotherapy discipline-specific in nature assuming these clinicians would be well-placed to report on available follow-up and rehabilitation services for post ICU survivors given their key role within the MDT, and involvement in patient care throughout the rehabilitation pathway. However as rehabilitation is a multidisciplinary intervention, surveying multiple members of the MDT responsible for delivering follow-up and rehabilitation may provide a more thorough and rounded picture of existing services, and the extent of multiprofessional involvement. It is possible that some respondents may have been unaware of available services if they were not directly involved in them, and furthermore barriers reported to offering services are reflective of one clinical discipline.

The content of the survey was designed to be as comprehensive as possible whilst reflecting the outline provided by NICE CG83 and the existing evidence-base. Therefore questions broadly summarised availability and content of follow-up services, but greater attention was paid to the detail of available post hospital discharge rehabilitation programmes which have been an area of growing research interest in recent years [177, 180, 185]. Existing published data regarding such programmes are limited [186], however it was anticipated that the survey would facilitate acquisition of information on programmes that were not part of previous or current research studies, assuming that local practice may well be in operation but less familiar outside of the host organisation. Exploring barriers to offering services provided an additional depth of information from those respondents who indicated these were not available although these were predominantly related to rehabilitation programmes, and not follow-up services.

7.4.3.2 Survey non-response

A strength of the current study is the employment of a variety of strategies to optimise survey completion and return, including promotional activities, inclusion of stamped addressed envelopes with all mailed surveys, and follow-up using telephone and email routes [350, 355, 356]. Adopting this approach resulted in a 76% response rate, considered to be an excellent return [355, 357, 358]. Higher response rates confer external validity [355]. Nonetheless, survey non-response is a challenge to the robustness of the current findings, and poses a major dilemma for researchers [358]. Non-response introduces a potential source of bias whereby it is unclear or often difficult to confirm whether non-respondents vary significantly from responders [357, 358]. Results require careful interpretation to consider how well they reflect the whole population, including those who failed to respond. Researchers can attempt to compare responders versus non-responders to demonstrate both groups are alike, albeit demographic or other data on which to do this may be limited [357, 358]. However despite the level of non-response in the current survey, 95% confidence intervals around results were relatively narrow confirming representativeness of responders to the general population of interest. The high response rate in the current study may represent the clinical concern of respondents with regard poor implementation of NICE CG83, in particular as the core standards for care of the critically ill patient have been recently published highlighting rehabilitation as an important core standard [359].

In addition, to minimise non-response five rounds of participant contact are recommended, a pre-notice letter of introduction, the initial survey, a thankyou or reminder, a repeat follow-up survey, and a final reminder [360]. Given the time constraints on busy senior clinicians working in the critical care environment, this extensive approach was considered excessive by the current study, and that it may feel overwhelming to recipients of this volume of correspondence such that it had the opposite effect and deterred response. It was also not pragmatic within the time and budgetary resources available. Instead survey distribution was accompanied by promotion on easily recognised and viewed forums to potential respondents including professional specialist interest group websites, conferences and interactive media.

Two rounds of postal distribution (approximately 40% response rate at each) were then followed by telephone and email (approximately 72% success rate).

7.5 Conclusion

Data from this first comprehensive UK survey of post hospital discharge follow-up and rehabilitation programmes for survivors of critical illness have demonstrated a low reported prevalence and a failure to implement NICE CG83. Lack of funding and clinical prioritisation was reported by clinicians as the major cause for this failure, but the paucity of evidence to underpin the guideline must be regarded as a major contributor to the discord between clinicians, managers and commissioners in delivery. Without clinical and cost effectiveness data, commissioning these services would be challenging in the current NHS climate. Clinical focus must be to ensure that guidelines have a robust evident base to maximise implementation and enhance patient care.

Chapter 8 Summary and Conclusions

8.1 Summary

Intensive care unit-acquired weakness (ICU-AW) is a significant complication of critical illness arising from peripheral skeletal muscle wasting and dysfunction. Residual physical functional impairment can be present for many years and can impact profoundly on recovery for ICU survivors. The primary aim of this thesis was to investigate the clinical assessment and treatment of ICU-AW. The studies centred on the utility of the Medical Research Council sum-score (MRC-SS) for diagnosing ICU-AW, the emergence of ultrasound as a technique to track peripheral skeletal muscle wasting during critical illness, exercise-based rehabilitation following hospital discharge for survivors of critical illness with ICU-AW, and the extent of UK implementation of national guidelines on the rehabilitation of post ICU patients.

The MRC-SS, a form of volitional manual muscle testing, is the most commonly reported volitional tool for the diagnosis of ICU-AW. Observational studies have associated presence of ICU-AW in patients at awakening, based on MRC-SS assessment, with prolonged mechanical ventilation and delayed weaning, respiratory muscle weakness, protracted ICU and hospital lengths of stay and increased mortality. Whilst inter-observer agreement of the MRC-SS has previously been established in healthy subjects mimicking weakness and stable post ICU patients in the recovery stage with high levels reported, determining agreement in patients whilst still in the ICU has proven more challenging with contrasting data reported particularly for ICU-AW diagnosis. In *Chapter 3*, a cohort of 20 ICU patients underwent MRC-SS testing by two experienced clinicians. High levels of inter-observer agreement were found (ICC 0.94 (95%CI 0.85-0.98)), but only moderate agreement for the diagnosis of ICU-AW (Kappa 0.6 (95%CI 0.25-0.95)). In comparison in a healthy individual who simulated a range of weakness presentations observed in the ICU cohort, close for both MRC-SS overall and agreement of ICU-AW diagnosis was evident (ICC 1.0 (95%CI 0.99-1.0) and Kappa 1.0 (95%CI 1.0-1.0) respectively).

As a diagnostic tool there have been no previous data reporting test characteristics of the MRC-SS. In a separate cohort of 94 patients, MRC-SS at awakening and clinical outcomes of ICU and hospital mortality and length of stay were prospectively

measured to evaluate the clinical predictive value of the measure. Eighteen patients died prior to awakening, and a further 11 were unable to perform the MRC-SS at awakening despite meeting screening criteria for suitable levels of consciousness and cognition. There was no association between ability to perform the test at awakening and clinical outcomes of ICU and hospital mortality and length of stay (all p=ns). In patients able to complete MRC-SS testing at awakening (n=65), prevalence of ICU-AW was 73.9%. There was no association evident between MRC-SS and ICU and hospital mortality (p=0.67 and 0.53 respectively), but a significant association was revealed for ICU and hospital length of stay (p=0.004 and p=0.04 respectively). Further analyses of test characteristics were therefore conducted demonstrating high sensitivity of the test (ICU LOS 92.9% (95%CI (76.5-99.1) and hospital LOS (84.2% (68.7-94.0)). However specificity and positive predictive value were poor across both outcomes. Receiver-operator characteristic analysis revealed no clinically meaningful MRC-SS thresholds, with sensitivity and specificity below acceptable levels.

Ultrasound of peripheral skeletal muscle architecture has recently emerged as an alternative effort-independent technique for monitoring the trajectory of muscle wasting in critically ill patients with a growing body of published data available. In the second study of this thesis (*Chapter 4*), data for quadriceps rectus femoris anatomical cross-sectional area (RF_{CSA}) demonstrated significant correlations with volitional (quadriceps maximum voluntary contraction) and non-volitional (twitch quadriceps) measures of quadriceps force at two measurement points along the length of the rectus femoris muscle (2/3 distance, r=0.6, p=0.002 for both, 3/5 distance, r=0.7, p=0.001 for both) in a cohort of healthy subjects. Using pennation angle data to derive physiological cross-sectional area failed to improve the strength of these correlations. Furthermore, there were no anthropomorphic factors found to be associated with pennation angle. High levels of both intra- and inter-observer agreement of ultrasound to measure RF_{CSA} were also demonstrated (n=5 healthy subjects, ICC 1.0 (95%CI 0.98-1.0) for 3/5 measuring distance, ICC 0.78 (95%CI 0.29-0.97) for 2/3 measuring distance, and n=20 ICU patients, ICC 0.99 (95%CI 0.97-0.99) respectively). These data support the technical application of ultrasound, in particular measures of peripheral skeletal muscle cross-sectional area, in the critically ill population and its use as a surrogate marker where strength cannot be measured.

However, a direct relationship between muscle size and force has yet to be established for this patient population.

Chapter 5 of this thesis builds on the aforementioned data from *Chapter 4* and presents a systematic review (PROSPERO database registration CRD42013004892) investigating the use of ultrasound for measurement of peripheral skeletal muscle architecture in critically ill patients. Adhering to PRISMA guidelines for conduct and reporting, findings from seven identified studies were extracted and synthesised, reporting various characteristics of peripheral skeletal muscle architecture measured, protocols for assessment and data describing muscle dysfunction. Meta-analyses of data were limited due to individual variability in included studies, however all studies reported data demonstrating the negative effects of critical illness on peripheral skeletal muscle. Whilst ultrasound demonstrates a number of technical and pragmatic advantages, data from one study demonstrated that ultrasound measures of peripheral skeletal muscle size underestimated changes evident on direct biopsy sampling of muscle tissue, highlighting that caution must be taken in interpreting results albeit this should not detract from the clinical utility of the technique.

Rehabilitation has been advocated in the management of ongoing physical functional impairment in survivors of critical illness. Early mobilisation is now common practice in many ICUs with ward-based intervention promoting restoration of functional levels in preparation for hospital discharge. Following hospital discharge service provision for post ICU patients is typically more inconsistent in availability. The feasibility of a post hospital discharge exercise-based rehabilitation programme for survivors of critical illness with ICU-AW was investigated in a pilot randomised controlled trial (RCT) (*Chapter 6*). Eligible patients included those with ICU-AW at ICU discharge based on MRC-SS assessment with intervention patients receiving a sixteen session exercise-based rehabilitation that commenced within two weeks of hospital discharge. Patients in the standard treatment arm received a weekly phone call in addition to standard care, which consists of no specific post ICU follow-up. Outcomes, including exercise capacity and health-related quality of life, were assessed at hospital discharge and at three months. In addition a parallel observational cohort study of those patients without ICU-AW was also performed.

In the RCT, no differences were observed between the standard treatment (n=10) and intervention groups (n=10) for any of the outcomes measured (all p=ns), although the study was not powered for this. In addition, and surprisingly, there was a variable pattern in terms of outcomes between the trial group and observational study cohort. These data do not support the use of the MRC-SS to categorise patients with a diagnosis of ICU-AW, and more specifically the MRC-SS test to diagnose ICU-AW was not a reliable indicator of physical functional or useful in identifying patients with ongoing rehabilitation needs and likely to respond to exercise-based rehabilitation treatment. A number of methodological factors were identified to enhance the design, conduct and analysis of a future trial, including development of an intervention effective above that of the trajectory of natural recovery. This is wholly important in the context of trials evaluating complex interventions delivered to complex patient groups.

In the final study of this thesis a national UK survey was conducted to determine implementation of NICE clinical guidelines detailing rehabilitation following critical illness at the post hospital discharge stage of patient pathway (*Chapter 7*). Data from two previous surveys indicated a low adherence to this guideline, albeit these were limited by level of detail and geographical coverage. In the current study, 240 organisations were identified from national databases, and a 76% response rate (182 responses) was achieved from across England, Wales, Scotland and Northern Ireland. Forty-eight (27.3%, 95%CI (20.7-33.9)) reported offering follow-up of post ICU patients at 2-3months as per NICE guidance, and only 12 offered a rehabilitation programme (6.8%, 95%CI (3.1-10.5)), of which 10 were in regular operation. Barriers to service provision were primarily funding, resource limitation and managerial prioritisation. These data highlight the current inadequacy of clinical services to address the ongoing health deficits in this patient population despite publication of national guidelines five years ago.

8.2 Future work

The work conducted in this thesis has highlighted a number of areas for further investigation. Specifically robust techniques for assessing muscle wasting and

weakness in critically ill patients are required as well as the delivery of optimal rehabilitation interventions for ICU survivors with ongoing physical functional impairment following hospital discharge. Volitional measurement of peripheral skeletal muscle strength demonstrates a number of caveats to their reliable use in critically ill patients. The technique of ultrasound as an alternative effort-independent technique is gaining increasing research popularity and has important clinical utility. However, whilst a relationship between muscle mass and muscle strength has previously been demonstrated in healthy subjects and patient groups, this relationship has yet to be determined for the critically ill population. Establishing the relationship between peripheral skeletal muscle mass, exercise capacity and physical function would offer additional validation of ultrasound as a surrogate marker in this setting and population.

A number of unanswered questions remain regarding the clinical field of rehabilitation for the post ICU patient population following hospital discharge. The 'PICO' approach (Population, Intervention, Control, Outcome) is beneficial to consider with regard these. Defining the target population of post critical illness patients requiring ongoing physical rehabilitation and likely to benefit from intervention has yet to be clarified. Eligibility criteria used for clinical trials may be too prescriptive in an attempt to standardise an inherently heterogeneous patient group, and those patients with clinical need may be excluded. Certainly use of manual muscle testing and the MRC-SS test to diagnose ICU-AW have been shown to have limited value in identifying those with ongoing rehabilitation requirements at hospital discharge. An alternative approach is to consider the population at an individual patient level and longitudinally track the trajectory of recovery with regular follow-up including a range of assessments to target the physical, psychological and cognitive impairments, and intervene with bespoke rehabilitation when natural recovery slows or reaches a plateau. In this way, both the timing and type of rehabilitation delivered is personalised to each individual patient. Although there may be considerable burden to healthcare systems to provide such an approach, this would be balanced by the potential for enhanced recovery post critical illness, minimising the cost and extent of healthcare utilisation that may otherwise occur in this patient group.

Defining the constituent components of a rehabilitation programme also remains unclear. Given the variability in nature and degree of impairment post critical illness, access to a multimodal package of interventions is most likely to be required although this requires further investigation and each component will need to be validated. In particular with regard physical interventions, the optimum 'dose' of effective exercise prescription remains unknown. Benchmarking of existing clinical services will accurately define the standard treatment arm of any future interventional trial, especially if multiple sites are to be involved. It will also allow evaluation of service implementation in line with established guidelines. Finally, defining the appropriate outcomes to determine clinical and cost effectiveness of an intervention is essential. Ideally, an agreed set of core outcome measures would be implemented across all clinical trials in the area of critical illness rehabilitation to represent the range of impairments evident.

8.3 Conclusion

Data from this thesis have demonstrated limitations to the use of volitional strength testing to diagnose ICU-AW in critically ill patients. Ultrasound of peripheral skeletal muscle architecture represents a feasible effort-independent alternative to monitor change in peripheral skeletal muscle during critical illness with clinical utility and a number of pragmatic advantages. Further work to confirm the relationship between peripheral skeletal muscle mass and force, and correlating this with exercise capacity, physical activity and physical function will strongly support its widespread use. Post critical illness patients can be considered as a highly complex patient group due to the wide variability in demographics, clinical diagnostic grouping and illness severity amongst patients combined with varying trajectories of recovery of physical, psychological and cognitive impairment. The delivery of an effective complex rehabilitation intervention that addresses these important clinical features represents a significant challenge for researchers and clinicians. Establishing a robust evidence-base from carefully designed interventional trials will facilitate improvement of services across the UK targeting the management of these critical care survivors.

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Publications and abstracts

PUBLICATIONS

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Appendices

Appendix I. Standard operating protocol for Medical Research Council sum-score

Supine position

Item	Protocol
Patient position	• Supine with 30° head elevation, with the exception of upright sitting for assessment of shoulder abduction (to allow for movement against gravity) • Remove all extra pillows • Ensure central, midline position determined by pelvic and shoulder symmetry
Order of testing of limb muscle group	• Distal to proximal anti-clockwise starting with right lower limb i.e. right lower limb, left lower limb, left upper limb, right upper limb • Shoulder abduction is the last muscle group assessed following repositioning (see above)
Passive range of movement assessment	• Allows for assessment of sensation, available joint range of movement, presence of velocity-dependent tonal changes that may influence measurement • Instruction to patient "Do not do anything, keep as relaxed as possible"
Active performance of muscle movement	• Allows for grading of muscle strength according to MRC scale • Observe and palpate muscle group for sign of activity (Levels 0 and 1) e.g. quadriceps for knee extension • Instruction to patient "Move your (limb segment) towards (appropriate direction) as much as you can and hold it there"
- Ankle dorsiflexion	- Tester fixes ankle with one hand to ensure midline position - Resistance applied along dorsum of foot with opposite hand for >Grade 3
- Knee extension	- Tester rests patient leg over their knee in flexed position, and fixes knee with one hand to ensure midline position - Resistance applied at distal two-thirds shin with opposite hand for >Grade 3
- Hip flexion	- Grade 3 = movement from supine to hip flexion achieving foot flat on bed - With hip in 90° hip flexion, resistance applied to mid thigh for >Grade 3
- Wrist extension	- Wrist is isolated by fixing the forearm above the joint line, in pronated position - Resistance applied over dorsum of hand for >Grade 3 - A pillow can be used, or the elbow can be flexed to 90° to bring the wrist joint into eyesight of patient if necessary

- Elbow flexion	- Tester ensures neutral midline forearm position; a pillow may be used to ensure upper arm is horizontal with body - Resistance is applied to the forearm for >Grade 3
- Shoulder abduction	- Elbow flexion is advised to create a shorter lever for movement, and to achieve a neutral scapular position with some horizontal flexion and external rotation as comfort requires - Grade 3 = 90° shoulder abduction - Resistance is applied to the upper arm for >Grade 3
'Break' test for >Grade 3	• Performed in mid- to inner-range of movement; this position can be demonstrated by tester • Instruction to patient "Hold your (limb segment) there, don't let me move you' • Force is gradually applied opposing the direction of limb segment movement, up to near maximal levels to 'break' patient resistance to movement • Grade 4 = On application of force, tester can 'break' the patient's static position • Grade 5 = on application of force, tester unable to move the body segment without involvement of other muscle groups/change in patient body position

Seated position

Item	Protocol
Patient position	• Upright sitting, as near to 90° as possible • Remove all extra pillows • Ensure central, midline position determined by pelvic and shoulder symmetry and knee position
Order of testing of limb muscle group	• Distal to proximal anti-clockwise starting with right lower limb i.e. right lower limb, left lower limb, left upper limb, right upper limb
Passive range of movement assessment	• Allows for assessment of sensation, available joint range of movement, presence of velocity-dependent tonal changes that may influence measurement • Instruction to patient "Do not do anything, keep as relaxed as possible"
Active performance of muscle movement	• Allows for grading of muscle strength according to MRC scale (Table E2a) • Observe and palpate muscle group for sign of activity (Levels 0 and 1) e.g. quadriceps for knee extension • Instruction to patient "Move your (limb segment) towards (appropriate direction)
- Ankle dorsiflexion	- Patient sits with hips in midline, knees flexed to mid-range and heels resting on stable surface - Testers kneels by patients and fixes ankle with one hand to ensure midline position - Resistance applied along dorsum of foot with opposite hand for >Grade 3
- Knee extension	- Patient sits with hips in midline, knees flexed to mid-range and heels resting on stable surface - Tester rests leg over their forearm to ensure support

	under knee in flexion, and fixes knee with one hand to ensure midline position - Resistance applied with other hand at distal two-thirds shin by applying body weight
- - Hip flexion	- Patient is seated with hips in passive flexion - Tester fixes at knee to ensure lower limb is in midline - Grade 3 = active movement beyond degree of passive seated hip flexion - Resistance is applied to patient's thigh for >Grade 3
- Wrist extension	- Forearm rests in pronation on a stable surface by patient - Tester stands perpendicular to patients and isolates wrist by fixing forearm above joint line - Resistance is applied through dorsum of hand for >Grade 3
- Elbow flexion	- Tested with elbow at patient's side in neutral pronation/supination - Resistance applied to forearm for >Grade 3
- Shoulder abduction	- Elbow flexion is advised to create a shorter lever for movement, and to achieve a neutral scapular position with some horizontal flexion and external rotation as comfort requires - Grade 3 = 90° shoulder abduction - Tester stands wide stance perpendicular to patient - Resistance is applied to the upper arm for >Grade 3
'Break' test for >Grade 3	• Performed in mid- to inner-range of movement; this position can be demonstrated by tester • Instruction to patient "Hold your (limb segment) there, don't let me move you' • Force is gradually applied opposing the direction of limb segment movement, up to near maximal levels to 'break' patient resistance to movement • Grade 4 = On application of force, tester can 'break' the patient's static position • Grade 5 = on application of force, tester unable to move the body segment without involvement of other muscle groups/change in patient body position

Appendix II. Short-Form 36 v2 Questionnaire (Acute Recall version)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past week</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past week</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past week</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix III. Hospital Anxiety and Depression Scale

HAD Scale

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he/she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and place a tick in the box opposite to the reply, which comes closes to how you have been feeling over the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

Tick on one box in each section

I feel tense or wound up

- Most of the time ☐
- A lot of the time ☐
- From time to time, occasionally ☐
- Not at all ☐

I still enjoy things I used to enjoy

- Definitely as much ☐
- Not quite so much ☐
- Only a little ☐
- Hardly at all ☐

I get a frightened feeling as if something awful is about to happen

- Very definitely & quite badly ☐
- Yes, but not too badly ☐
- A little, but it doesn't worry me ☐
- Not at all ☐

I can laugh & see the funny side of things

- As much as I always could ☐
- Not quite so much now ☐
- Definitely not so much now ☐
- Not at all ☐

Worrying thoughts go through my mind

- A great deal of the time ☐
- A lot of the time ☐
- From time to time but not that often ☐
- Only occasionally ☐

I feel cheerful

- Not at all ☐
- Not often ☐
- Sometimes ☐
- Most of the time ☐

I can sit at ease and feel relaxed

- Definitely ☐
- Usually ☐
- Not often ☐
- Not at all ☐

I feel as if I am slowed down

- Nearly all the time ☐
- Very often ☐
- Sometimes ☐
- Not at all ☐

I get a frightened feeling like 'butterflies in the stomach'

- Not at all ☐
- Occasionally ☐
- Quite often ☐
- Very often ☐

I have lost interest in my appearance

- Definitely ☐
- I don't take as much care as I should ☐
- I may not take as much care ☐
- I take just as much care as ever ☐

I feel restless as if I have to be on the move

- Very much indeed ☐
- Quite a lot ☐
- Not very much ☐
- Not at all ☐

I look forward with enjoyment to things

- As much as I ever did ☐
- Rather less than I used to ☐
- Definitely less than I used to ☐
- Hardly at all ☐

I get sudden feelings of panic

- Very often indeed ☐
- Quite often ☐
- Not very often ☐
- Hardly at all ☐

I can enjoy a good book or radio or TV programme

- Often ☐
- Sometimes ☐
- Not often ☐
- Very seldom ☐

Appendix IV. Systematic review search strategies (Chapter 5)

Search strategies for electronic databases used in this systematic review are presented below (Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, Excerpta Medica Database (EMBASE), Web of Science and Cochrane). Searching Scopus resulted in no results (search strategy not reported), and searches were not storable in the Physiotherapy Evidence Database (PEDro) however the search involved terms used in the summaries below.

CINAHL search strategy (EbscoHost)

S15 S7 and S10 and S14
S14 S11 OR S12 OR S13
S13 muscle*
S12 (MH "Muscle, Skeletal")
S11 muscle wasting OR muscle mass OR cross-sectional area OR fibre pennation angle OR pennation angle OR muscle thickness OR muscle layer thickness OR echo intensity OR echogenicity OR muscle architecture
S10 S8 OR S9
S9 ultrasound OR ultrasonography
S8 (MH "Ultrasonography")
S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6
S6 intensive care OR critical care OR critical illness OR ICU OR critically ill OR multi-organ failure OR sepsis
S5 (MH "Sepsis")
S4 (MH "Multiple Organ Dysfunction Syndrome")
S3 (MH "Intensive Care Units")
S2 (MH "Critical Illness") OR (MH "Critically Ill Patients")
S1 (MH "Intensive Care Units") OR (MH "Critical Care")

MEDLINE search strategy (OvidSp)

1. intensive care/
2. critical illness/
3. intensive care/ or intensive care unit/
4. sepsis/ or multiple organ failure/ or septic shock/
5. sepsis/
6. (intensive care or critical care or critical illness or ICU or critically ill or multi-organ failure or sepsis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
7. 1 or 2 or 3 or 4 or 5 or 6
8. (ultrasonography or ultrasound).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

9. muscle mass/ or muscle weakness/ or skeletal muscle/ or muscle/ or muscle atrophy/
10. muscle mass/
11. muscle/ or ultrasound/ or muscle atrophy/
12. muscle thickness/ or thickness/ or muscle/
13. skeletal muscle/ or muscle atrophy/
14. (muscle* or muscle wasting or muscle mass or cross-sectional area or fibre pennation angle or pennation angle or muscle thickness or muscle layer thickness or echo intensity or echogenicity or muscle architecture).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
15. 9 or 10 or 11 or 12 or 13 or 14
16. ultrasound/
17. 8 or 16
18. 7 and 15 and 17

EMBASE search strategy (OvidSp)

1. intensive care/
2. critical illness/
3. intensive care unit/
4. critically ill patient/
5. multiple organ failure/
6. sepsis/
7. (intensive care or critical care or critical illness or ICU or critically ill or multi-organ failure or sepsis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. ultrasound/
10. (ultrasound or ultrasonography).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
11. 9 or 10
12. muscle/
13. muscle atrophy/
14. muscle mass/
15. muscle thickness/
16. (muscle* or muscle wasting or muscle mass or cross-sectional area or fibre pennation angle or pennation angle or muscle thickness or muscle layer thickness or echo intensity or echogenicity or muscle architecture).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
17. 12 or 13 or 14 or 15 or 16
18. 8 and 11 and 17

Web of Science search strategy (Web of Knowledge)

#4 #3 AND #2 AND #1

#3 Topic=(muscle* OR muscle wasting OR muscle mass OR cross-sectional area OR fibre pennation angle OR pennation angle OR muscle thickness OR muscle layer thickness OR echo intensity OR echogenicity OR muscle architecture)

#2 Topic=(ultrasound OR ultrasonography)

#1 Topic=(intensive care OR critical care OR critical illness OR ICU OR critically ill OR multi-organ failure OR sepsis)

Cochrane search strategy (Cochrane)

#1 intensive care or critical care or critical illness or ICU or critically ill or multi-organ failure or sepsis:ti, ab, kw

#2 ultrasound or ultrasonography:ti, ab, kw

#3 muscle* or muscle wasting or muscle mass or cross-sectional are or fibre pennation angle or pennation angle or muscle thickness or muscle layer thickness or echo intensity or echogenicity or muscle architecture:ti, ab, kw

#4 MeSH descriptor: (Intensive Care) explode all trees

#5 MeSH descriptor: (Critical Care) explode all trees

#6 MeSH descriptor: (Critical Illness) explode all trees

#7 MeSH descriptor: (Critical Illness) explode all trees

#8 MeSH descriptor: (Sepsis) explode all trees

#9 MeSH descriptor: (Ultrasonograhpy) explode all trees

#10 MeSH descriptor: (Muscles) explode all trees

#11 #4 and #5 and #6 and #7 and #8

#12 #1 or #11

#13 #3 or #10

#14 #2 and #9

#15 #14 and #13 and #12

Appendix V. Rehabilitation following critical illness survey (Chapter 7)

SECTION 1 YOUR CRITICAL CARE SERVICES

1) Is your hospital a: Teaching (University) hospital □

District General hospital □

Other □

2) Please indicate the number, size and speciality of any critical care areas in your hospital (include all individual intensive care unit (ICU, Level 3), high dependency unit (HDU, Level 2) and/or combined Level areas)

CC area	Level	Speciality	Beds
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

SECTION 2 FOLLOW-UP FOR POST CRITICAL ILLNESS PATIENTS

Are you involved in follow-up for post critical illness patients 2-3 months after discharge?

YES □ **(please go to Question 1.)** **NO** □ **(please go to SECTION 3)**

1. What form does this follow-up take:

   ICU follow-up clinic □

   Medical outpatient appointment (as part of other medical follow-up) □

   Telephone call □

   Postal survey □

   Rehabilitation class □

   Other (please specify)

   .....

2. Who is involved in this follow-up?

   Physiotherapist □ Occupational Therapist □

   Critical Care Nurse □ Critical Care Doctor □

   Psychologist □ Dietician □

   Other (please specify)

   .....

3. Does this follow-up involve a functional reassessment based on previous assessment at hospital discharge?

   YES □ NO □

4. What else is covered in this follow-up?

   Exercise capacity □ Health-related quality of life □

   Psychological status □ Nursing-related issues □

   Medical status □ Diet/nutrition □

   Other (please specify)

   .....

SECTION 3 REHABILITATION SERVICES FOLLOWING CRITICAL ILLNESS

Does your hospital offer a rehabilitation programme following hospital discharge specifically for post critical illness patients as part of *routine* clinical practice?

(separate to generic services such as intermediate care, supported discharge, hospital-at-home or similar)

YES □ **(please go to Question 1.)** **NO** □ **(please go to Question 19.)**

---

1. Who is responsible for leading this rehabilitation programme?

Physiotherapist	□	Critical Care Doctor	□
Occupational Therapist	□	Critical Care Nurse	□
Speech and Language Therapist	□	Exercise/sports therapist	□
Other (please give detail)	□		

.....

2. If a physiotherapist, is this.....

ICU physiotherapist	□	Rehabilitation physiotherapist	□
Current banding/position		.....	
Duration of ICU rehabilitation experience		.....	

3. How do you select patients for inclusion into the programme?

		Assessment measure (if applicable)
Duration of mechanical ventilation in ICU	□	.....
Duration of ICU admission	□	.....
Duration of hospital admission	□	.....
Physical function at ICU discharge	□	.....
Muscle strength at ICU discharge	□	.....
Exercise capacity at ICU discharge	□	.....
Health-related quality of life at ICU discharge	□	.....
Physical function at hospital discharge	□	.....
Muscle strength at hospital discharge	□	.....

Exercise capacity at hospital discharge □ .....

Health-related quality of life at hospital discharge □ .....

Not applicable – all post ICU patients are eligible □ .....

Other/comments (please give detail)

.....

FORMAT OF DELIVERY

4. Is your programme:

Home-based □ Hospital-based □ Community-based □

Other/comments (please give detail)

.....

5. In your programme, do patients exercise:

Under supervision □ Independently □ Combination □

Do you use an accompanying rehabilitation or exercise manual YES □ NO □

Other/comments (please give detail)

.....

6. Is your programme:

A stand-alone programme for post critical illness patients □

Part of existing rehabilitation services including patients with other disease groups □

If so which .....

Other/comments (please give detail)

.....

7. At what time point post hospital discharge does the programme commence:

Immediately post hospital discharge □ One week post hospital discharge □

Two weeks post hospital discharge □ One month post hospital discharge □

2-3 months post hospital discharge □

Other/comments (please give detail)

.....

Does your service have a waiting list: YES □ NO □

If so, how long? .....

STRUCTURE

8. How many sessions are in the rehabilitation programme e.g. 12 sessions, 16 sessions?

   .....

9. How often are the sessions?

   Weekly □ Twice-weekly □ Fortnightly □

   Other
   .....

10. How long is each session?

    30 minutes □ 45minutes □ 1 hour □

    Other
    .....

11. Is this a: Rolling programme □ Stand alone □

12. How many patients are in the group? .....

    What is the staff:patient ratio? .....

13. Do patients exercise in a: Pre-determined circuit □ Patient-specific plan □

    Other
    .....

CONTENT

14. Does your rehabilitation programme include an exercise component

    YES □ (please continue) NO □
    (please go to Question 17.)

    What exercises are included (please tick all that apply)?

Cardiovascular	Strength	Balance	Functional
Step-ups □	Lower limb □	Static □	Sit-to-stand □
Treadmill □	Upper limb □	Dynamic□	Timed Up and Go□
Static bike □	Free weights □		Walking □
Cross-trainer□	Theraband/ resisted □ □		

Other/comments (please give detail)

.....

How are these exercises prescribed?

Results of walking tests	□	Results of balance assessment	□
Results of physical function assessment	□	Repetition maximum principle	□
Target heart rate	□	Target Borg (please specify range)	□
Clinician judgement	□		

Other/comments (please give detail)

.....

15. How do you monitor and/or progress exercise intensity during the exercise session?

Heart rate targets	□	SpO_2	□	Borg	□
Visual analogue scale	□	Clinical observation/judgement of patient			□
Patient verbal feedback	□	No formal monitoring			□
Reassessment of baseline measures	□				

Other/comments (please give detail)

.....

16. Does your rehabilitation programme include an education component

YES □ NO □

If YES....what topics are included

Subject		Delivered by (please list MDT member)
Exercise	□	.....
Stress management	□	.....
Nutrition	□	.....
Return to work	□	.....
Energy conservation	□	.....
Medications	□	.....
What to expect of recovery	□	.....
Motivational coaching/training	□	.....

Other (please give detail)

.....

EVALUATION

17. What outcome measures do you use with patients participating in your rehabilitation programme?

    Strength-based e.g. repetition maximum, maximum weight □

    Please specify.....

    Exercise capacity e.g. field walking tests (e.g. 6 Minute Walk Test, cardiopulmonary exercise testing (VO_2max) □

    Please specify.....

    Health-related quality of life e.g. SF-36 survey, Hospital Anxiety and Depression scale □

    Please specify.....

    Mental/cognitive assessment e.g. Montreal Cognition Assessment □

    Please specify.....

    Functional performance e.g. Timed Up and Go, Short Physical Performance Battery □

    Please specify.....

    Other (please specify)

    .....

18. Any other comments regarding your post critical illness rehabilitation programme?
    .....

    .....

    .....

NO AVAILABLE REHABILITATION SERVICE

19. If the answer to offering a rehabilitation service/programme at the start of this section was' NO' please give details as to limiting factors for availability of these services.

	All reasons (tick all that apply)	**Main reason** (tick one only)
Lack of sufficient staff numbers	□	□
Lack of suitably trained staff	□	□
Lack of available space/venue	□	□
No evidence to suggest benefit	□	□
Lack of funding	□	□
Not considered required service at managerial level	□	□
Insufficient patient numbers to justify	□	□
Not sure what to include in a rehabilitation programme	□	□
Resources prioritised to other patient groups/clinical areas	□	□
Extra-contractual (out-of-area) patient caseload	□	□

Other (please specify)

.....

20. Do you refer ICU patients routinely into other rehabilitation programmes/services, either in-patient or community-based?

YES □ (please continue) NO □ (please go to Question 21.)

Pulmonary rehabilitation □ Cardiac rehabilitation □
Exercise on prescription (or similar) □ Community gym sessions □
Other (please specify)

.....

21. Does your organisation offer a post hospital discharge rehabilitation programme to survivors of critical illness as part of a research study?

YES □ NO □

If able, please provide contact detail for lead researcher

.....

(End of survey – many thanks for completing)